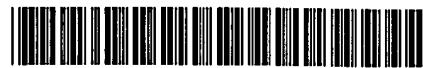




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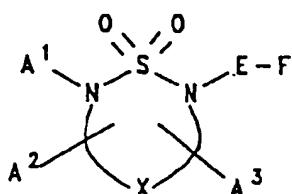
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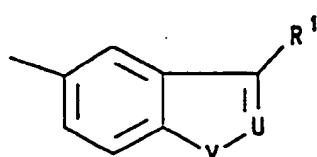
(54) Substituted cyclic sulphamide derivatives.

(57) Compounds of formula I, or a salt or prodrug thereof:



wherein

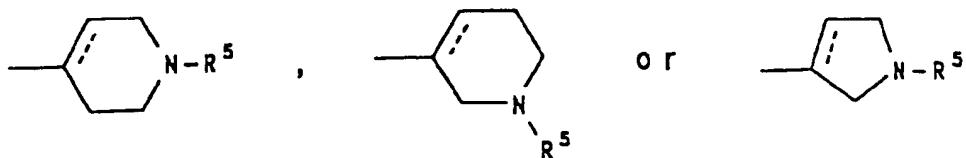
- X- represents -(CH₂)_m- in which m is 2 or 3;
A¹ represents hydrogen, hydrocarbon or a heterocyclic group;
A² and A³ independently represent hydrogen or C₁₋₈ alkyl;
E represents a bond or a straight or branched alkylene chain containing from 1 to 4 carbon atoms;
and
F represents a group of formula



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in which

- U represents nitrogen or C-R²;
V represents oxygen, sulphur or N-R³;
R¹ represents -(CH₂)_pCHR⁴.NR⁶R⁷ or a group of formula



in which the broken line represents an optional chemical bond;

p is 1 or 2; and

R², R³, R⁴, R⁵, R⁶ and R⁷ independently represent hydrogen or C₁₋₆ alkyl.

The derivatives are selective agonists of 5-HT₁-like receptors and are therefore useful in the treatment of clinical conditions, in particular migraine and associated disorders, for which a selective agonist of these receptors is indicated.

The present invention relates to a class of substituted cyclic sulphamide derivatives which act on 5-hydroxytryptamine (5-HT) receptors, being selective agonists of so-called "5-HT₁-like" receptors. They are therefore useful in the treatment of clinical conditions for which a selective agonist of these receptors is indicated.

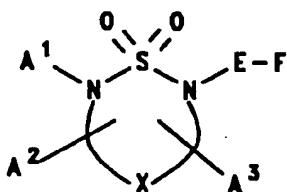
5 5-HT₁-like receptor agonists which exhibit selective vasoconstrictor activity have recently been described as being of use in the treatment of migraine (see, for example, A. Doenicke et al., *The Lancet*, 1988, Vol. 1, 1309-11). The compounds of the present invention, being selective 5-HT₁-like receptor agonists, are accordingly of particular use in the treatment of migraine and associated conditions, e.g. cluster headache, chronic paroxysmal hemicrania, headache associated with vascular disorders, tension headache and paediatric migraine.

10 EP-A-0313397 describes a class of tryptamine derivatives substituted by a five-membered heteroaliphatic ring, which are stated to be specific to a particular type of "5-HT₁-like" receptor and thus to be effective therapeutic agents for the treatment of clinical conditions, particularly migraine, requiring this activity. GB-A-2083463 describes a class of *inter alia* tryptamine derivatives substituted by an aminosulphonylamino or aminosulphonylaminooalkyl moiety, which compounds are stated to be potentially useful for the treatment of migraine. However, neither of these publications discloses or suggests the substituted cyclic sulphamide derivatives provided by the present invention.

15 The present invention provides a compound of formula I, or a salt or prodrug thereof:

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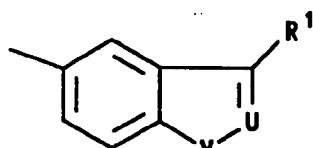
(1)

wherein

35 -X- represents -(CH₂)_m- in which m is 2 or 3;
 A¹ represents hydrogen, hydrocarbon or a heterocyclic group;
 A² and A³ independently represent hydrogen or C₁-₆ alkyl;
 E represents a bond or a straight or branched alkylene chain containing from 1 to 4 carbon atoms; and
 F represents a group of formula

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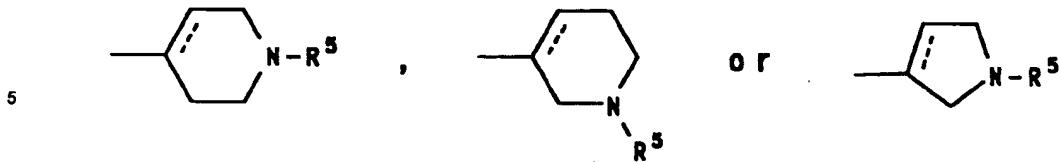
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in which

50 U represents nitrogen or C-R²;
 V represents oxygen, sulphur or N-R³;
 R¹ represents -(CH₂)_pCHR⁴.NR⁶R⁷ or a group of formula

55



- 10 in which the broken line represents an optional chemical bond;

p is 1 or 2; and

R², R³, R⁴, R⁵, R⁶ and R⁷ independently represent hydrogen or C₁₋₆ alkyl.

For use in medicine, the salts of the compounds of formula I will be non-toxic pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their non-toxic pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable non-toxic acid such as hydrochloric acid, fumaric acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g. sodium or potassium salts; alkaline earth metal salts, e.g. calcium or magnesium salts; and salts formed with suitable organic ligands, e.g. quaternary ammonium salts.

The term "hydrocarbon" as used herein includes straight-chained, branched and cyclic groups containing up to 18 carbon atoms, suitably up to 15 carbon atoms, and conveniently up to 12 carbon atoms. Suitable hydrocarbon groups include C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl(C₁₋₆)alkyl, aryl and aryl(C₁₋₆)alkyl.

The expression "a heterocyclic group" as used herein includes cyclic groups containing up to 18 carbon atoms and at least one heteroatom preferably selected from oxygen, nitrogen and sulphur. The heterocyclic group suitably contains up to 15 carbon atoms and conveniently up to 12 carbon atoms, and is preferably linked through carbon. Examples of suitable heterocyclic groups include C₃₋₇ heterocycloalkyl, C₃₋₇ heterocycloalkyl(C₁₋₆)alkyl, heteroaryl and heteroaryl(C₁₋₆)alkyl groups.

Suitable alkyl groups include straight-chained and branched alkyl groups containing from 1 to 6 carbon atoms. Typical examples include methyl and ethyl groups, and straight-chained or branched propyl and butyl groups. Particular alkyl groups are methyl, ethyl, isopropyl and t-butyl.

Suitable alkenyl groups include straight-chained and branched alkenyl groups containing from 2 to 6 carbon atoms. Typical examples include vinyl and allyl groups.

Suitable alkynyl groups include straight-chained and branched alkynyl groups containing from 2 to 6 carbon atoms. Typical examples include ethynyl and propargyl groups.

Suitable cycloalkyl groups include groups containing from 3 to 7 carbon atoms. Particular cycloalkyl groups are cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

A particular aryl group is phenyl.

Particular aryl(C₁₋₆)alkyl groups include benzyl, phenethyl and phenylpropyl.

Suitable heterocycloalkyl groups include asetidinyl, pyrrolidyl, piperidyl, piperazinyl and morpholinyl groups.

Suitable heteroaryl groups include pyridyl, quinolyl, isoquinolyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyranyl, furyl, benzofuryl, dibenzofuryl, thieryl, benzthienyl, imidazolyl, oxadiazolyl and thiadiazolyl groups.

A particular heteroaryl(C₁₋₆)alkyl group is pyridylmethyl.

The hydrocarbon and heterocyclic groups may in turn be optionally substituted by one or more groups selected from C₁₋₆ alkyl, phenyl, halogen, C₁₋₆ haloalkyl, C₁₋₆ aminoalkyl, trifluoromethyl, hydroxy, C₁₋₆ alkoxy, aryloxy, keto, C₁₋₃ alkyleneoxy, nitro, cyano, carboxy, C₂₋₆ alkoxy carbonyl, C₂₋₆ alkoxy carbonyl-(C₁₋₆)alkyl, C₂₋₆ alkyl carbonyloxy, aryl carbonyloxy, C₂₋₆ alkyl carbonyl, aryl carbonyl, C₁₋₆ alkylthio, C₁₋₆ alkylsulphinyl, C₁₋₆ alkylsulphonyl, arylsulphonyl, -NR^VR^W, -NR^VCOR^W, -NR^VCO₂R^W, -NR^VSO₂R^W, -CH₂NR^VSO₂R^W, -NHCONR^VR^W, -CONR^VR^W, -SO₂NR^VR^W and -CH₂SO₂NR^VR^W, in which R^V and R^W independently represent hydrogen, C₁₋₆ alkyl, aryl or aryl(C₁₋₆)alkyl, or R^V and R^W together represent a C₂₋₆ alkylene group.

When R^V and R^W together represent a C₂₋₆ alkylene group, this group may be an ethylene, propylene, butylene, pentamethylene or hexamethylene group, preferably butylene or pentamethylene.

The term "halogen" as used herein includes fluorine, chlorine, bromine and iodine, especially fluorine.

The present invention includes within its scope prodrugs of the compounds of formula I above. In general, such prodrugs will be functional derivatives of the compounds of formula I which are readily convertible *in vivo* into the required compound of formula I. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

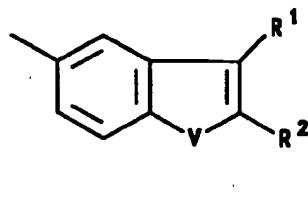
Where the compounds according to the invention have at least one asymmetric centre, they may accordingly exist as enantiomers. Where the compounds according to the invention possess two or more asymmetric centres, they may additionally exist as diastereoisomers. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention.

The alkylene chain E may be, for example, methylene, ethylene, 1-methylethylene, propylene or 2-methylpropylene. Alternatively, the group E may represent a single bond such that the group F in formula I is attached directly to the cyclic sulphamide moiety.

The group F is suitably an indole, benzofuran or benzothiophene moiety of formula FA, or an indazole moiety of formula FB:

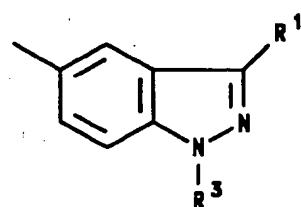
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(FA)

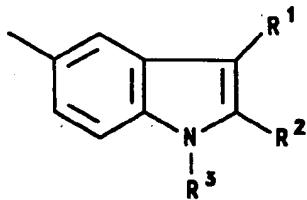


(FB)

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wherein V, R¹, R² and R³ are as defined above. Preferably, the group F represents an indole moiety of structure FC:

35



40

(FC)

wherein R¹, R² and R³ are as defined above, in particular wherein R² and R³ are both hydrogen.

Suitable values for the group A¹ include hydrogen, and C₁₋₆ alkyl, C₃₋₇ cycloalkyl, aryl, aryl(C₁₋₆)alkyl, C₃₋₇ heterocycloalkyl, heteroaryl or heteroaryl(C₁₋₆)alkyl, any of which groups may be optionally substituted. Examples of optional substituents on the group A¹ suitably include trifluoromethyl, C₁₋₆ alkoxy, C₂₋₆ alkoxycarbonyl, C₂₋₆ alkylcarbonyl, C₁₋₆ alkylsulphonyl, arylsulphonyl, amino, mono- or di(C₁₋₆)-alkylamino, C₂₋₆ alkylcarbonylamino, arylcarbonylamino, C₂₋₆ alkoxycarbonylamino, C₁₋₆ alkylsulphonylamino, arylsulphonylamino, C₁₋₆ alkylsulphonylaminomethyl, aminocarbonylamino, mono- or di(C₁₋₆)-alkylaminocarbonylamino, mono- or diarylaminocarbonylamino, pyrrolidylcarbonylamino, aminocarbonyl, mono- or di(C₁₋₆)-alkylaminocarbonyl, C₁₋₆ alkylaminosulphonyl, aminosulphonylmethyl, and mono- or di(C₁₋₆)-alkylaminosulphonylmethyl.

Representative values of A¹ include hydrogen, methyl, ethyl, aminoethyl, acetylaminooethyl, benzoylaminooethyl, methoxycarbonylaminoethyl, ethoxycarbonylaminoethyl, t-butoxycarbonylaminoethyl, methylsulphonylaminoethyl, aminocarbonylaminoethyl, methylaminocarbonylaminoethyl, t-butylaminocarbonylaminoethyl, phenylaminocarbonylaminoethyl, pyrrolidylcarbonylaminoethyl, isopropyl, cyclopropyl,

phenyl, methylsulphonylaminophenyl, aminocarbonylphenyl, methylaminocarbonylphenyl, methylsulphonylaminomethylphenyl, aminosulphonylmethylphenyl, methylaminosulphonylmethylphenyl, dimethylaminosulphonylmethylphenyl, benzyl, trifluoromethylbenzyl, methoxybenzyl, acetylaminobenzyl, methylsulphonylaminobenzyl, aminocarbonylaminobenzyl, aminocarbonylbenzyl, methylaminocarbonylbenzyl, methylsulphonylbenzyl, methylaminosulphonylbenzyl, pyridylmethyl and methoxypyridylmethyl. Particular values of A¹ include hydrogen, methyl, ethyl, isopropyl, benzyl and acetylaminobenzyl.

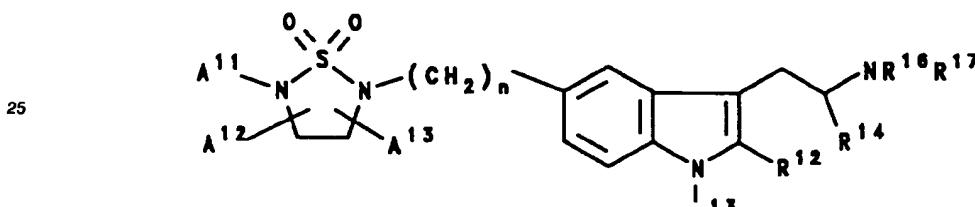
The groups A² and A³ independently represent hydrogen or C₁₋₆ alkyl. The alkyl moiety is suitably a methyl or ethyl group, or a straight-chained or branched propyl, butyl, pentyl or hexyl group. Preferably, one of A² and A³ represents hydrogen and the other represents hydrogen or C₁₋₆ alkyl, especially hydrogen or methyl. Where A² and A³ are both other than hydrogen, it is preferred that these groups are identical. Moreover, where A² and A³ are both other than hydrogen, it is particularly preferred that these groups are both attached to the same carbon atom, i.e. giving rise to gem-dialkyl substitution.

Representative values of R¹ include aminoethyl, N-methylaminoethyl, N,N-dimethylaminoethyl, 4-piperidyl, 1-methyl-4-piperidyl, 3-pyrrolidinyl and 1-methyl-3-pyrrolidinyl. Preferably, R¹ represents aminoethyl, N-methylaminoethyl or N,N-dimethylaminoethyl.

Preferred values for the groups R² to R⁷ are hydrogen and methyl.

A particular sub-class of compounds according to the invention is represented by the compounds of formula IIA, and salts and prodrugs thereof:

20



30

wherein

35 n is zero, 1, 2 or 3, preferably zero, 1 or 2;

A¹¹ represents hydrogen; or C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₇ cycloalkyl, aryl, aryl(C₁₋₆)-alkyl, C₃₋₇ heterocycloalkyl, heteroaryl or heteroaryl(C₁₋₆)alkyl, any of which groups may be optionally substituted; and

40 A¹², A¹³, R¹², R¹³, R¹⁴, R¹⁵ and R¹⁷ independently represent hydrogen or C₁₋₆ alkyl.
Examples of optional substituents on the group A¹¹ suitably include trifluoromethyl, C₁₋₆ alkoxy, C₂₋₆ alkoxy carbonyl, C₂₋₆ alkylcarbonyl, C₁₋₆ alkylsulphonyl, arylsulphonyl, amino, mono- or di(C₁₋₆)-alkylamino, C₂₋₆ alkylcarbonylamino, arylcarbonylamino, C₂₋₆ alkoxy carbonylamino, C₁₋₆ alkylsulphonylamino, arylsulphonylamino, C₁₋₆ alkylsulphonylaminomethyl, aminocarbonylamino, mono- or di(C₁₋₆)-alkylaminocarbonylamino, mono- or diarylaminocarbonylamino, pyrrolidylcarbonylamino, aminocarbonyl, mono- or di(C₁₋₆)-alkylaminocarbonyl, C₁₋₆ alkylaminosulphonyl, aminosulphonylmethyl, and mono- or di(C₁₋₆)-alkylaminosulphonylmethyl.

45 Particular values of A¹¹ with respect to formula IIA include hydrogen, methyl, ethyl, isopropyl, benzyl and acetylaminobenzyl.

50 Preferably one of A¹² and A¹³ represents hydrogen and the other represents hydrogen or methyl, especially hydrogen. Alternatively, when A¹² and A¹³ are both other than hydrogen, it is preferred that they are both methyl groups attached to the same carbon atom.

55 Preferably, R¹², R¹³ and R¹⁴ each represents hydrogen. Preferred values of R¹⁵ and R¹⁷ with respect to formula IIA include hydrogen and methyl.

Specific compounds within the scope of the present invention include: 3-[2-(dimethylamino)ethyl]-5-[(1,1-dioxo-5-methyl-1,2,5-thiadiazolidin-2-yl)methyl]-1H-indole;
3-(2-aminoethyl)-5-[(1,1-dioxo-5-methyl-1,2,5-thiadiazolidin-2-yl)methyl]-1H-indole;
3-[2-(dimethylamino)ethyl]-5-[2-(1,1-dioxo-5-methyl-1,2,5-thiadiazolidin-2-yl)ethyl]-1H-indole;
3-(2-aminoethyl)-5-[2-(1,1-dioxo-5-methyl-1,2,5-thiadiazolidin-2-yl)ethyl]-1H-indole;

- 3-[2-(dimethylamino)ethyl]-5-[(5-(4-acetylaminobenzyl)-1,1-dioxo-1,2,5-thiadiazolidin-2-yl)methyl]-1H-indole;
 3-(2-aminoethyl)-5-[(5-(4-acetylaminobenzyl)-1,1-dioxo-1,2,5-thiadiazolidin-2-yl)methyl]-1H-indole;
 3-(2-aminoethyl)-5-[(1,1-dioxo-1,2,5-thiadiazolidin-2-yl)methyl]-1H-indole;
 3-(2-aminoethyl)-5-[(1,1-dioxo-5-isopropyl-1,2,5-thiadiazolidin-2-yl)methyl]-1H-indole;
 5 3-(2-aminoethyl)-5-[2-(1,1-dioxo-1,2,5-thiadiazolidin-2-yl)ethyl]-1H-indole;
 3-(2-aminoethyl)-5-[2-(1,1-dioxo-5-ethyl-1,2,5-thiadiazolidin-2-yl)ethyl]-1H-indole;
 3-[2-(dimethylamino)ethyl]-5-[(1,1-dioxo-1,2,5-thiadiazolidin-2-yl)methyl]-1H-indole;
 3-[2-(dimethylamino)ethyl]-5-[(1,1-dioxo-5-isopropyl-1,2,5-thiadiazolidin-2-yl)methyl]-1H-indole;
 3-[2-(dimethylamino)ethyl]-5-[2-(1,1-dioxo-1,2,5-thiadiazolidin-2-yl)ethyl]-1H-indole;
 10 3-[2-(dimethylamino)ethyl]-5-[2-(1,1-dioxo-5-ethyl-1,2,5-thiadiazolidin-2-yl)ethyl]-1H-indole;
 3-[2-(methylamino)ethyl]-5-[(1,1-dioxo-5-methyl-1,2,5-thiadiazolidin-2-yl)methyl]-1H-indole;
 3-(2-aminoethyl)-5-[(1,1-dioxo-6-methyl-3,4,5,6-tetrahydro-1,2,6-thiadiazin-2-yl)methyl]-1H-indole;
 3-[2-(dimethylamino)ethyl]-5-[(1,1-dioxo-6-methyl-3,4,5,6-tetrahydro-1,2,6-thiadiazin-2-yl)methyl]-1H-indole;
 3-(2-aminoethyl)-5-[(4,4-dimethyl-1,1-dioxo-1,2,5-thiadiazolidin-2-yl)methyl]-1H-indole;
 15 3-(2-aminoethyl)-5-[(3,3-dimethyl-1,1-dioxo-1,2,5-thiadiazolidin-2-yl)methyl]-1H-indole;
 3-(2-aminoethyl)-5-(1,1-dioxo-5-methyl-1,2,5-thiadiazolidin-2-yl)-1H-indole;
 3-(2-aminoethyl)-5-(5-benzyl-1,1-dioxo-1,2,5-thiadiazolidin-2-yl)-1H-indole;
 3-[2-(dimethylamino)ethyl]-5-[(4,4-dimethyl-1,1-dioxo-1,2,5-thiadiazolidin-2-yl)methyl]-1H-indole;
 3-[2-(dimethylamino)ethyl]-5-[(3,3-dimethyl-1,1-dioxo-1,2,5-thiadiazolidin-2-yl)methyl]-1H-indole;
 20 3-[2-(dimethylamino)ethyl]-5-(1,1-dioxo-5-methyl-1,2,5-thiadiazolidin-2-yl)-1H-indole;
 3-[2-(dimethylamino)ethyl]-5-(5-benzyl-1,1-dioxo-1,2,5-thiadiazolidin-2-yl)-1H-indole;
 and salts and prodrugs thereof.

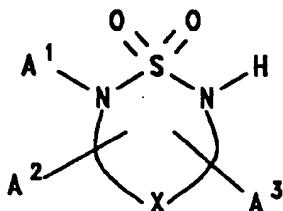
The invention also provides pharmaceutical compositions comprising one or more compounds of this invention in association with a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, auto-injector devices or suppositories; for oral, parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tabling ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

45 The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone or gelatin.

In the treatment of migraine, a suitable dosage level is about 0.01 to 250 mg/kg per day, preferably about 0.05 to 100 mg/kg per day, and especially about 0.05 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day.

50 The compounds according to this invention may be prepared by a process which comprises reacting a compound of formula W-E-F with a compound of formula III:

5



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(III)

15 wherein X, A¹, A², A³, E and F are as defined above, and W represents a group which is capable of being displaced during the course of the reaction.

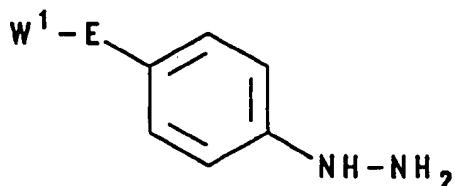
The displaceable group W suitably represents hydroxy, in which case the reaction is advantageously carried out in the presence of triphenylphosphine and diethyl azodicarboxylate, ideally in an organic solvent such as tetrahydrofuran at room temperature.

20 Alternatively, the group W may be a conventional leaving group such as a halogen atom, for example bromine, or a trialkylammonium group, for example trimethylammonium. Where W represents bromine, the reaction is conveniently carried out in the presence of a mild base, e.g. potassium carbonate, suitably in an organic solvent such as N,N-dimethylformamide, at a temperature of between 10°C and 100°C, ideally at room temperature. Where W represents trimethylammonium, the reaction is conveniently carried out in the presence of a strong base such as sodium hydride, suitably in an organic solvent such as N,N-dimethylformamide, and ideally at a temperature in the region of 90°C.

25 Where they are not commercially available, the intermediates of formula W-E-F may be prepared by procedures analogous to those described in the accompanying Examples, or by methods well known from the art. For example, those compounds wherein W is halogen and E is other than a bond may be prepared from the corresponding compounds of formula W-E-F in which W is hydroxy using standard halogenation techniques. Alternatively, those compounds wherein W is a trialkylammonium group may be prepared from the corresponding compounds of formula W-E-F in which W represents dialkylamino by quaternisation using a suitable alkyl iodide in conventional manner.

30 Where the group F is an indole moiety of structure FC as defined above, the compound of formula W-E-F may be prepared by reacting a compound of formula IV:

40



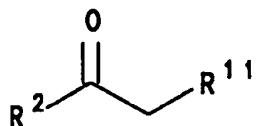
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(IV)

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wherein W¹ corresponds to the group W as defined above, or represents a protected derivative thereof or a precursor thereto; and E is as defined above; with a compound of formula V or a carbonyl-protected form thereof:

55



(V)

10 wherein R² is as defined above and R¹¹ corresponds to the group R¹ as defined above or represents a group of formula -CH₂.CHR⁴D¹, in which R⁴ is as defined above and D¹ represents a readily displaceable group; followed, where required, by (i) N-alkylation by standard methods to introduce the moiety R³, and (ii) deprotection or interconversion of the moiety W¹ to the desired group W.

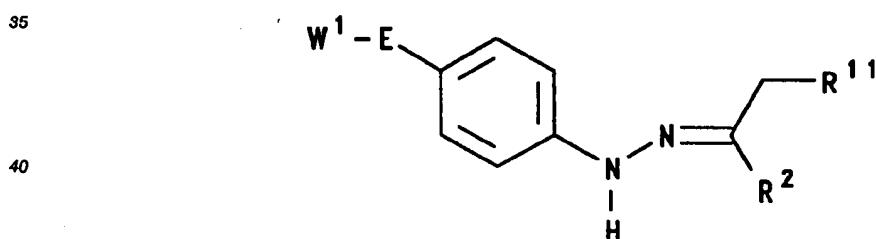
15 Where the moiety W¹ in the compounds of formula IV represents a precursor to a hydroxy group, this is suitably a C₁-4 alkyl ester group, e.g. methoxycarbonyl or ethoxycarbonyl, which can subsequently be converted to the required hydroxy group by reduction using, for example, diisobutylaluminium hydride (DIBAL-H) in tetrahydrofuran at -30 °C.

20 Alternatively, where W¹ represents the precursor to a trialkylammonium group, this is suitably a cyano moiety, which can subsequently be reduced by catalytic hydrogenation; the resulting aminomethyl group can in turn be alkylated, and finally quaternised using a suitable alkyl iodide, to afford the desired trialkylammonium group.

25 Suitable carbonyl-protected forms of the compounds of formula V include the dimethyl acetal or ketal derivatives.

30 The readily displaceable group D¹ in the compounds of formula V suitably represents a halogen group, preferably chlorine. When the moiety R¹¹ in the compounds of formula V is a group of formula -CH₂.CHR⁴D¹, the substituent D¹ is displaced in situ under the prevailing reaction conditions to afford a final product of formula I wherein R¹ represents a group of formula -CH₂.CHR⁴.NH₂. The terminal amino group can subsequently, if desired, be further elaborated using techniques known from the art to give a compound of formula I wherein R¹ represents the required group of formula -CH₂.CHR⁴.NR⁶R⁷.

The reaction of compounds IV and V may be carried out in a single step (Fischer indole synthesis) or by an initial non-cyclising step at a lower temperature to give a compound of formula VI:



40

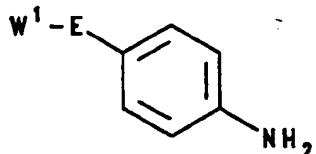
(VI)

45 wherein W¹, E, R² and R¹¹ are as defined above; followed by cyclisation using a suitable reagent, such as a polyphosphate ester.

50 The hydrazines of formula IV may be prepared from the corresponding anilines of formula VII:

55

5



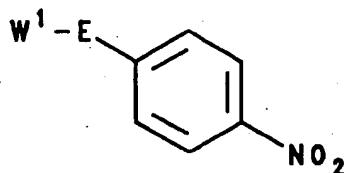
(VII)

10

wherein W^1 and E are as defined above; by diazotisation followed by reduction. Diazotisation is typically carried out using sodium nitrite/conc. HCl and the resulting diazo product reduced *in situ* using, for example, tin(II) chloride/conc. HCl.

15 The anilines of formula VII may be prepared by reduction of the corresponding nitro compounds of formula VIII:

20



25

(VIII)

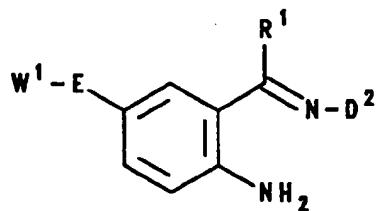
30 wherein W^1 and E are as defined above; typically by catalytic hydrogenation or using tin(II) chloride.

Where they are not commercially available, the nitro compounds of formula VIII may be synthesized by standard methods well known to those skilled in the art.

Where the group F is an indazole moiety of structure FB as defined above, the compound of formula W-E-F may be prepared by the cyclisation of a compound of formula IX:

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40



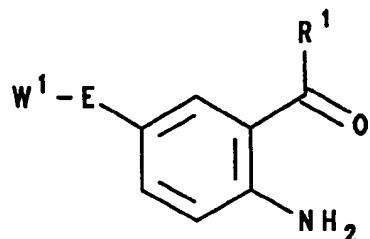
45

(IX)

wherein W^1 , E and R^1 are as defined above; and D^2 represents a readily displaceable group; followed, where required, by (i) N-alkylation by standard methods to introduce the moiety R^3 , and (ii) deprotection or interconversion of the moiety W^1 to the desired group w.

The cyclisation of compound IX is conveniently achieved in a suitable organic solvent at an elevated temperature, for example in a mixture of m-xylene and 2,6-lutidine at a temperature in the region of 140°C.

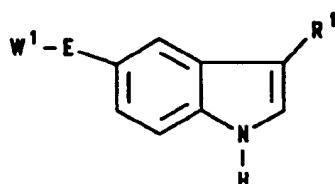
55 The readily displaceable group D^2 in the compounds of formula IX suitably represents a C_{1-4} alkanoyloxy group, preferably acetoxy. Where D^2 in the desired compound of formula IX represents acetoxy, this compound may be conveniently prepared by treating a carbonyl compound of formula X:



(x)

- 15 wherein R¹, E and W¹ are as defined above; or a protected derivative thereof; with hydroxylamine hydrochloride, advantageously in pyridine at the reflux temperature of the solvent; followed by acetylation with acetic anhydride, advantageously in the presence of a catalytic quantity of 4-dimethylaminopyridine, in dichloromethane at room temperature.

20 The N-formyl protected derivative of the intermediate of formula X may be conveniently prepared by ozonolysis of an indole derivative of formula XI:

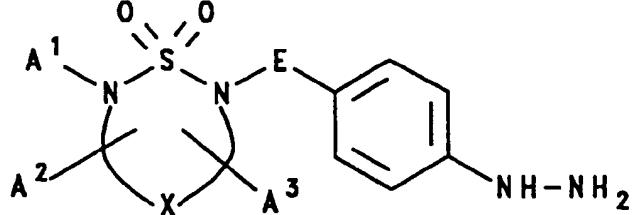


(xii)

- wherein R¹, E and W¹ are as defined above; followed by a reductive work-up, advantageously using dimethyl sulphide.

The indole derivative of formula XI may be prepared by methods analogous to those described in the accompanying Examples, or by procedures well known from the art.

In an alternative process, the compounds according to the invention wherein the group F is an indole moiety of formula FC as defined above may be prepared by a method which comprises reacting a compound of formula XII:

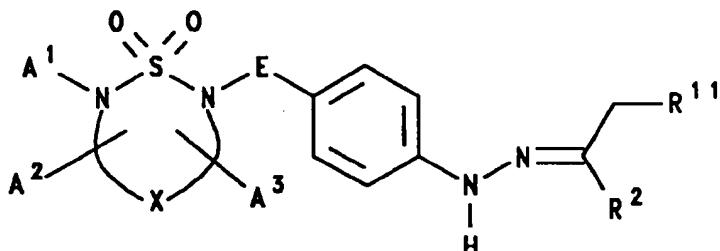


(XII)

- 55 wherein X, A¹, A², A³ and E are as defined above; with a compound of formula V as defined above, or a carbonyl-protected form thereof, e.g. the dimethyl acetal or ketal; followed, where required, by N-alkylation by standard methods to introduce the moiety R³.

As with that between compounds IV and V, the reaction between compounds XII and V may be carried out in a single step (Fischer indole synthesis) or by an initial non-cyclising step at a lower temperature to give a compound of formula XIII:

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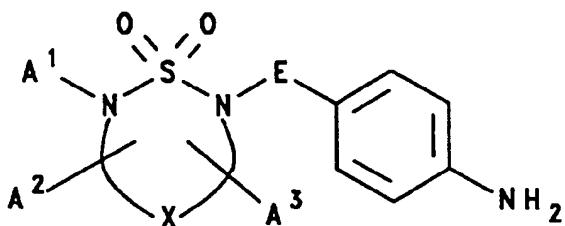
10

(XIII)

wherein X, A¹, A², A³, E, R² and R¹¹ are as defined above; followed by cyclisation using a suitable reagent, e.g. a polyphosphate ester.

20 The hydrazines of formula XII may be prepared from the corresponding anilines of formula XIV:

25



30

(XIV)

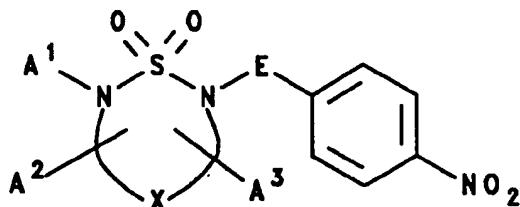
35

wherein X, A¹, A², A³ and E are as defined above; by methods analogous to those described above with reference to the compounds of formula VII.

The anilines of formula XIV may be prepared by reduction of the corresponding nitro compounds of formula XV:

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45



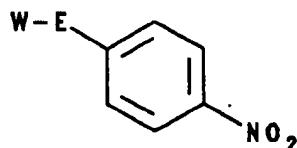
50

(XV)

wherein X, A¹, A², A³ and E are as defined above; typically by catalytic hydrogenation or using tin (II) chloride.

55 The intermediates of formula XV may be prepared by reaction of a compound of formula III as defined above with a compound of formula XVI:

5



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(XVI)

wherein W and E are as defined above; under reaction conditions analogous to those described above for the reaction between the compound of formula $\text{W}-\text{E}-\text{F}$ and the compound of formula III.

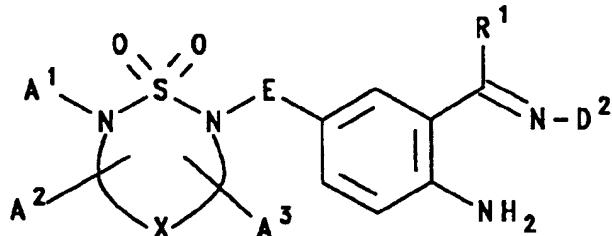
When the moiety W in the compounds of formula XVI is attached directly to the aromatic ring, i.e. when E represents a bond, it is preferred that W represents fluorine. In this case, the reaction is conveniently carried out in the presence of sodium hydride using N,N -dimethylformamide as solvent, ideally at the reflux temperature of the solvent.

Where they are not commercially available, the nitro compounds of formula XVI may be synthesized by standard methods well known to those skilled in the art.

In a further process, the compounds according to the invention wherein the group F is an indazole moiety of formula FB as defined above may be prepared by a method which comprises cyclising a compound of formula XVII:

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35

(XVII)

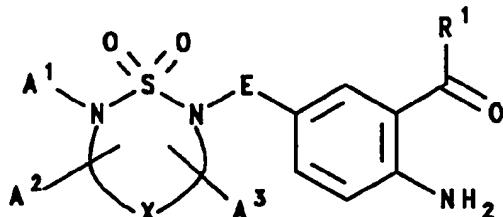
wherein X , A^1 , A^2 , A^3 , E , R^1 and D^2 are as defined above; followed, where required, by N-alkylation by standard methods to introduce the moiety R^3 .

As with the cyclisation of compound IX, that of compound XVII is conveniently achieved in a suitable organic solvent at an elevated temperature, for example in a mixture of *m*-xylene and 2,6-lutidine at a temperature in the region of 140°C .

The compounds of formula XVII may, for example, be prepared from the corresponding compound of formula XVIII:

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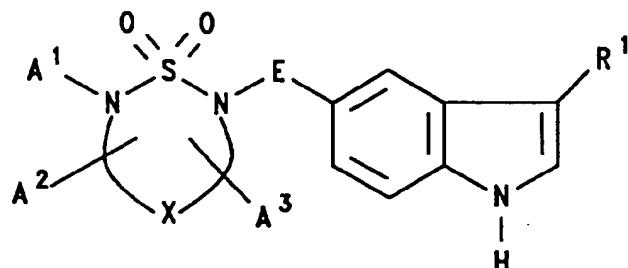
55



(XVIII)

wherein X, A¹, A², A³, E and R¹ are as defined above; or a protected derivative thereof; which in turn may be prepared from the corresponding compound of formula XIX:

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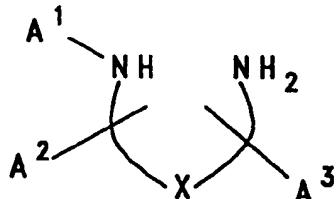
(XIX)

wherein X, A¹, A², A³, E and R¹ are as defined above; using methods analogous to those described above with reference to the compounds of formulae X and XI. Thus, for example, since W¹ in the compounds of formula XI represents or is convertible into a group W, the compounds of formula XIX may be prepared therefrom by reaction with a compound of formula III.

The intermediates of formula III may be prepared by a method based on those described in Indian J. Chem., 1982, 21B, 941, and Chem. Ber., 1978, 111, 1915. In essence, this comprises reacting a compound of formula XX with a compound of formula XXI:

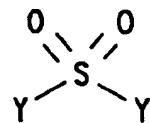
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(XX)



(XXI)

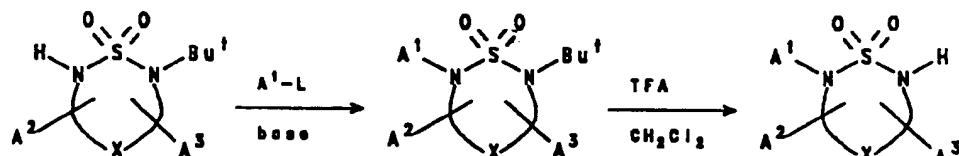
40 wherein X, A¹, A² and A³ are as defined above; and Y represents halogen, e.g. chlorine, or amino.

Where Y represents halogen, the reaction is conveniently carried out in chloroform at -50°C. Alternatively, where Y represents amino, the reaction is conveniently carried out in pyridine at reflux.

In a variant of this method, a compound of formula III wherein A¹ is t-butyl may be converted into a desired compound of formula III wherein A¹ is other than t-butyl by means of the following sequence:

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50



55

(III)

wherein A¹, A², A³ and X are as defined above; L represents a leaving group such as halogen, e.g. chlorine; and TFA is an abbreviation for trifluoroacetic acid. A suitable base for use in the first step of the sequence is potassium carbonate.

- It will be understood that any compound of formula I initially obtained from any of the above processes may, where appropriate, subsequently be elaborated into a further compound of formula I by techniques known from the art. For example, a compound of formula I wherein R³ is hydrogen initially obtained may be converted into a compound of formula I wherein R³ represents C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl by standard techniques such as alkylation, for example by treatment with an alkyl iodide, e.g. methyl iodide, typically under basic conditions, e.g. sodium hydride in dimethylformamide, or triethylamine in acetonitrile. Similarly, a compound of formula I wherein R¹ represents a group of formula -CH₂.CHR⁴.NH₂ initially obtained may be converted into a compound of formula I wherein R¹ represents a group of formula -CH₂.CHR⁴.NR⁶R⁷ in which R⁶ and R⁷ are as defined above with the exception of hydrogen, for example by conventional N-alkylation or N-arylation techniques, e.g. by treatment with the appropriate aldehyde in the presence of a reducing agent such as sodium cyanoborohydride. Alternatively, a compound of formula I wherein R¹ represents a group of formula -CH₂.CHR⁴.NHMe can be prepared from the corresponding N-formyl derivative by reduction with borane-tetrahydrofuran complex.

Where the above-described processes for the preparation of the compounds according to the invention give rise to mixtures of stereoisomers, these isomers may be separated by conventional techniques such as preparative chromatography.

- The novel compounds may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. The novel compounds may, for example, be resolved into their component enantiomers by standard techniques, such as the formation of diastereomeric pairs by salt formation with an optically active acid, such as (-)-di-p-toluoyl-d-tartaric acid and/or (+)-di-p-toluoyl-1-tartaric acid followed by fractional crystallization and regeneration of the free base. The novel compounds may also be resolved by formation of diastereomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary.

- During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in Protective Groups in Organic Chemistry, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, 1981. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

The following Examples illustrate the preparation of compounds according to the invention.

- The ability of test compounds to bind to 5-HT₁-like receptors was measured in membranes prepared from pig caudate using the procedure described in J. Neurosci., 1987, 7, 894. Binding was determined using 2 nM 5-hydroxytryptamine creatinine sulphate, 5-[1,2-³H(N)] as a radioligand. Cyanopindolol (100 nM) and mesulergine (100 nM) were included in the assay to block out 5-HT_{1A} and 5-HT_{1C} binding sites respectively. The concentration of the compounds of the accompanying Examples required to displace 50% of the specific binding (IC₅₀) is below 1 μM in each case.

- The activity of test compounds as agonists of the 5-HT₁-like receptor was measured in terms of their ability to mediate contraction of the saphenous vein of New Zealand White rabbits, using the procedure described in Arch. Pharm., 1990, 342, 111. Agonist potencies were calculated as -log₁₀EC₅₀ (pEC₅₀) values, from plots of percentage 5-HT (1 μM) response against the concentration of the agonist. The compounds of the accompanying Examples were found to possess pEC₅₀ values in this assay of not less than 5.0 in each case.

INTERMEDIATE I

3-[2-(N-Tert-butyloxycarbonylamino)ethyl]-5-hydroxymethyl-1H-indole

- 1.4-Carbethoxyphenylhydrazine Hydrochloride

- To a cooled (-13 °C) and stirred suspension of ethyl 4-aminobenzoate (100g, 605.3mmol) in concentrated hydrochloric acid (780ml) was added dropwise a solution of sodium nitrite (43.9g, 635.9mmol) in water (312ml) at such a rate as to keep the temperature below -4 °C (ca 50 minutes). After being stirred for further 10 minutes at -5 °C, the mixture was quickly filtered to remove solids and the clear yellow filtrate was added portionwise to a cooled (-20 °C) and stirred solution of tin (II) chloride dihydrate (682.9g, 3.02mmol) in concentrated hydrochloric acid (470ml) at such a rate as to maintain the temperature below

-10 °C (ca 25 minutes). The resulting mixture was allowed to warm to -5 °C over 25 min and the solid was collected by filtration, washed with diethyl ether (2 x 300ml) and dried over phosphorous pentoxide - potassium hydroxide at 60 °C in vacuum oven to give 131.8g (100%) of the title compound as a white solid. A sample recrystallised from absolute ethanol showed: mp 208-212 °C (needles); δ_H (360MHz, DMSO-d₆) 10.42 (3H, br s, -NH₃⁺), 8.92 (1H, br s, -NH-), 7.86 (2H, d, J = 8.8Hz, Ar-H), 7.01 (2H, d, J = 8.8Hz, Ar-H), 4.26 (2H, q, J = 7.1Hz, -OCH₂-), 1.30 (3H, t, J = 7.1Hz, -CH₃); m/z (Cl) 181(M⁺ + 1).

2. Ethyl 3-(2-aminoethyl)-1H-indole-5-carboxylate. Hydrochloride

A solution of 4-carbethoxyphenylhydrazine hydrochloride (130g, 598mmol) and 4-chlorobutanal dimethylacetal (86.6g, 568mmol) in ethanol-water (5:1, 4L) was stirred at room temperature for 20 minutes and then it was heated at reflux for 4.5 hours. Solvents were removed under vacuum, the remaining residue was dissolved in hot ethanol (1L) and products were precipitated by addition of diethyl ether (1.5L). The solid was filtered off and recrystallised from a mixture of hot ethanol (200ml) and acetone (1L) to give 55.4g (34.5%) of the title compound as a pale yellow solid; δ_H (360MHz, DMSO-d₆) 11.43 (1H, s, indole N-H), 8.26 (1H, s, Ar-H), 8.03 (3H, br s, -NH₃⁺), 7.73 (1H, dd, J = 8.6 and 1.6Hz, Ar-H), 7.45 (1H, d, J = 8.6Hz, Ar-H), 7.38 (1H, d, J = 2.2Hz, Ar-H), 4.32 (2H, q, J = 7.1Hz, -OCH₂-), 3.06 (4H, s, -CH₂CH₂-), 1.34 (3H, t, J = 7.1Hz, -CH₃); m/z (Cl) 231 (M⁻ - 1).

20 3. Ethyl 3-[2-(N-tert-butyloxycarbonylamino)ethyl]-1H-indole-5-carboxylate

To a cooled (-10 °C) and stirred suspension of ethyl 3-(2-aminoethyl)-1H-indole-5-carboxylate hydrochloride (26.9g, 100mmol) in anhydrous dichloromethane (900ml) was added anhydrous triethylamine (28.7ml, 200mmol) followed by di-tert-butylcarbonate (24.0g, 110mmol) and the resulting mixture was stirred at that temperature for 30 minutes and at room temperature for 3 hours, under nitrogen. The reaction mixture was diluted with dichloromethane (300ml), washed with 2N hydrochloric acid (2x 100ml), 10% aqueous sodium bicarbonate (100ml), brine (100ml), dried (MgSO₄) and concentrated. Flash chromatography (silica gel, dichloromethane - methanol, 96:4) of the residue followed by crystallisation of the product from absolute ethanol gave 23.3g (70%) of the required title compound as white crystals; mp 170-171 °C; δ_H (360MHz, CDCl₃) 8.35 (1H, s, Ar-H), 8.28 (1H, br s, indole N-H), 7.91 (1H, dd, J = 8.5 and 1.6Hz, Ar-H), 7.36 (1H, d, J = 8.5 Hz, Ar-H), 7.09 (1H, br s, Ar-H), 4.61 (1H, br s, -NH-), 4.40 (2H, q, J = 7.2Hz, -OCH₂-), 3.48 (2H, m, -CH₂N-), 2.16 (2H, t, J = 6.8Hz, -CH₂-), 1.43 (9H, s, t-Bu), 1.42 (3H, t, J = 7.2Hz, -CH₃); m/z (El) 332 (M⁺). (Found: C, 65.27; H, 7.59; N, 8.40. C₁₈H₂₄N₂O₄ requires: C, 65.04; H, 7.28; N, 8.43%).

35 4. 3-[2-(N-Tert-butyloxycarbonylamino)ethyl]-5-hydroxymethyl-1H-indole

To a cooled (-50 °C) and stirred solution of the product from Step 3 (17.4g, 52.4mmol) in anhydrous tetrahydrofuran (650ml) was added dropwise via cannula diisobutylaluminium hydride (1M in toluene; 168ml) over 23 minutes, under a nitrogen atmosphere. After being stirred at -25 °C for 1 hour, additional diisobutylaluminium hydride (1M in toluene; 40ml) was added dropwise over 15 minutes and stirring was continued at -25 °C for further 30 minutes. Methanol (65ml) was added dropwise (CAUTION! H₂ evolution) at -35 °C followed by aqueous citric acid (10%; 450ml) and the organic phase was decanted off. The aqueous solution was extracted with ethyl acetate (500ml) and the combined organic phases were washed with brine (1x 200ml), dried (Na₂SO₄) and concentrated. Flash chromatography (silica gel, dichloromethane - methanol, 97:3) of the remaining residue gave 13.8g (90.8%) of the title compound as a white solid. A sample recrystallised from dichloromethane showed: mp 129-130 °C; δ_H (360MHz, DMSO-d₆) 10.70 (1H, br s, indole N-H), 7.44 (1H, s, Ar-H), 7.28 (1H, d, J = 8.3Hz, Ar-H), 7.10 (1H, s, Ar-H), 7.03 (1H, d, J = 8.3Hz, Ar-H), 6.86 (1H, br t, -NH-), 4.95 (1H, t, J = 5.6Hz, -OH), 4.54 (2H, d, J = 5.6Hz, -CH₂OH), 3.18 (2H, m, -CH₂N-), 2.78 (2H, t, J = 7.2 Hz, -CH₂-), 1.38 (9H, s, t-Bu); m/z (El) 290 (M⁺). (Found: C, 65.95; H, 7.82; N, 9.37. C₁₆H₂₂N₂O₃ requires: C, 66.18; H, 7.64; N, 9.65%).

INTERMEDIATE 2

3-[2(N-Tert-butyloxycarbonylamino)ethyl]-5-(2-hydroxyethyl)-1H-indole

55 1. 4-(Carbethoxymethyl)phenylhydrazine Hydrochloride

The title compound was prepared from ethyl 4-aminophenylacetate by a similar method to that

described for Intermediate 1 (Step 1); mp 171-174 °C (absolute ethanol); δ_H (360MHz, DMSO-d₆) 10.02 (br s, -N⁺H₃), 8.14 (br s, -NH-), 7.16 (2H, d, J = 8.5Hz, Ar-H), 6.92 (2H, d, J = 8.5Hz, Ar-H), 4.06 (2H, q, J = 7.1Hz, -OCH₂-), 3.56 (2H, s, Ar-CH₂-), 1.17 (3H, t, J = 7.1Hz, -CH₃); m/z (EI) 194 (M⁺).

5 2. Ethyl 3-(2-aminoethyl)-1H-indole-5-acetate. Hydrochloride

The title compound was prepared from 4-(carbethoxymethyl)phenylhydrazine hydrochloride and 4-chlorobutanal dimethylacetal by a similar method to that described for Intermediate 1 (Step 2); mp 204-206 °C (ethanol/diethyl ether); δ_H (360MHz, DMSO-d₆) 10.70 (1H, br s, indole N-H), 8.09 (3H, br s, -N⁺H₃), 7.43 (1H, s, Ar-H), 7.31 (1H, d, J = 8.3Hz, Ar-H), 7.23 (1H, d, J = 2.3Hz, Ar-H), 6.99 (1H, dd, J = 8.3 and 1.6Hz, Ar-H), 4.07 (2H, q, J = 7.1Hz, -OCH₂-), 3.68 (2H, s, Ar-CH₂CO-), 3.02 (4H,m, -CH₂CH₂-), 1.18 (3H, t, J = 7.1Hz, -CH₃); m/z (Cl) 247 (M⁺+1).

15 3. Ethyl 3-[2-(N-tert-butyloxycarbonylamino)ethyl]-1H-indole-5-acetate

The title compound was prepared in 98% yield from ethyl 3-(2-aminoethyl)-1H-indole-5-acetate by a similar method to that described for Intermediate 1 (Step 3); colourless thick oil; δ_H (360MHz, CDCl₃), 8.06 (1H, br s, indole N-H), 7.48 (1H, s, Ar-H), 7.30 (1H, d, J = 8.3Hz, Ar-H), 7.13 (1H, d, J = 8.3Hz, Ar-H), 6.99 (1H, s, Ar-H), 4.58 (1H, br s, -NH-), 4.15 (2H, q, J = 7.1Hz, -OCH₂-), 3.70 (2H, s, Ar-CH₂-CO-), 3.45 (2H, m, -CH₂N-), 2.92 (2H, t, J = 6.8Hz, -CH₂-), 1.43 (9H, s, t-Bu), 1.25 (3H, t, J = 7.1Hz, -CH₃); m/z (EI) 346 (M⁺).

4. 3-[2-(N-Tert-butyloxycarbonylamino)ethyl]-5-(2-hydroxyethyl)-1H-indole

Diisobutylaluminium hydride reduction of ethyl 3-[2-(N-tert-butyloxycarbonylamino)ethyl]-1H-indole-5-acetate using the conditions described for Intermediate 1 (Step 4) afforded the title compound as a colourless thick oil, after purification by flash chromatography (silica gel, diethyl ether); δ_H (250MHz, CDCl₃) 8.03 (1H, br s, indole N-H), 7.44 (1H, s, Ar-H), 7.32 (1H, d, J = 8.3Hz, Ar-H), 7.07 (1H, dd, J = 8.3 and 1.6Hz, Ar-H), 7.02 (1H, d, J = 2.2Hz, Ar-H), 4.60 (1H, br s, -NH-), 3.89 (2H, t, J = 6.5Hz, -CH₂OH), 3.45 (2H, m, -CH₂N-), 2.97 (2H, t, J = 6.5Hz, -CH₂CH₂OH), 2.93 (2H, t, J = 6.8Hz, -CH₂-), 1.43 (9H, s, t-Bu); m/z (Cl) 303 (M⁻¹). (Found: m/z 304.1759. C₁₇N₂O requires: m/z 304.1787).

INTERMEDIATE 3

3-[2-(N-Tert-butyloxycarbonylamino)ethyl]-5-trimethylammoniummethyl-1H-indole Iodide

35 1. 4-Cyanophenylhydrazine. Hydrochloride

To a cooled (-15 °C) and stirred suspension of 4-aminobenzonitrile (50g, 423mmol) in concentrated hydrochloric acid (550ml) was added dropwise a solution of sodium nitrite (31.5g, 457mmol) in water (200ml) at such a rate as to maintain the temperature below -10 °C. After the addition was finished, the reaction mixture was quickly filtered to remove solids and the filtrate was added portionwise to a cooled (-20 °C) and stirred solution of tin (II) chloride dihydrate (477g, 2.1mol) in concentrated hydrochloric acid (370ml) at such a rate as to maintain the temperature below -10 °C. After further 15 minutes at -10 to 0 °C, the white precipitate was collected by filtration, washed with diethyl ether (4 x 250ml) and dried to give 56g (78%) of the title compound; mp 235-237 °C (ethanol-water 1:1); δ_H (250MHz, DMSO-d₆) 10.50 (3H, br s, -N⁺H₃), 9.10 (1H, br s, -NH-), 7.71 (2H, d, J = 8.8Hz, Ar-H), 7.03 (2H, d, J = 8.8Hz, Ar-H); m/z (Cl) 132 (M⁻¹).

50 2. 3-(2-Aminoethyl)-5-cyano-1H-indole. Hydrochloride

To a stirred suspension of 4-cyanophenylhydrazine (50g) in a mixture of ethanol and water (5:1; 21) was added 4-chlorobutanal dimethylacetal (45g) and the resulting mixture was refluxed for 18 hours. Solvents were removed under vacuum and the residue was azeotroped with toluene to give a brown solid. Crystallisation of this crude material from methanol (150ml) gave 23g (35%) of the title compound as a yellow solid; mp 270-274 °C; δ_H (250MHz, DMSO-d₆) 11.60 (1H, br s, indole N-H), 8.17 (1H, d, J = 1.1Hz, Ar-H), 7.97 (3H, br s, -N⁺H₃), 7.54 (1H, d, J = 8.5Hz, Ar-H), 7.46 (1H, s, Ar-H), 7.44 (1H, dd, J = 8.5 and 1.1Hz, Ar-H), 3.05 (4H, br s, -CH₂CH₂N-); m/z (Cl) 184 (M⁻¹).

3. 3-[2-(N-Tert-butyloxycarbonylamino)ethyl]-5-cyano-1H-indole

The title compound was prepared in 58% yield from 3-(2-aminoethyl)-5-cyano-1H-indole hydrochloride using the conditions described for Intermediate 1 (Step 3); white solid; mp 132-134 °C (hexane-ethyl acetate); δ_H (250MHz, CDCl₃) 8.42 (1H, br s, indole N-H), 7.93 (1H, s, Ar-H), 7.41 (2H, s, Ar-H), 7.12 (1H, d, J = 2.2Hz, Ar-H), 4.71 (1H, br s, -NH-), 3.44 (2H, q, J = 6.9Hz, -CH₂NH-), 2.94 (2H, t, J = 6.9Hz, Ar-CH₂-), 1.45 (9H, s, t-Bu); m/z (Cl) 286 (M⁺ + 1).

4. 5-Aminomethyl-3-[2-(N-tert-butyloxycarbonylamino)ethyl]-1H-indole

A solution of the product from the previous step (11.3g) in a mixture of absolute ethanol (750ml) and chloroform (22ml) was hydrogenated at 50 psi over platinum (IV) oxide (1g) for 28 hours. The catalyst was removed by filtration and solvents were removed under vacuum. Flash chromatography of the residue (silica gel, dichloromethane-methanol-ammonia 90:10:1) gave 9.5g (82%) of the title compound as a white solid; mp 147-149 °C; δ_H (360MHz, CDCl₃) 8.04 (1H, br s, indole N-H), 7.52 (1H, s, Ar-H), 7.33 (1H, d, J = 8.4Hz, Ar-H), 7.16 (1H, d, J = 8.4Hz, Ar-H), 7.03 (1H, s, Ar-H), 4.61 (1H, br s, -NHBOC), 3.96 (2H, s, Ar-CH₂NH₂), 3.45 (2H, br q, -CH₂NHBOC), 2.95 (2H, t, J = 6.8Hz, Ar-CH₂-), 1.43 (9H, s, t-Bu); m/z (Cl) 288 (M⁺ - 1).

5. 3-[2-(N-Tert-butyloxycarbonylamino)ethyl]-5-dimethylaminomethyl-1H-indole

The title compound was prepared in 71% yield from 5-aminomethyl-3-[2-(N-tert-butyloxycarbonylamino)ethyl]-1H-indole using the conditions described for Example 2; colourless thick oil; δ_H (250MHz, CDCl₃) 8.07 (1H, br s, indole N-H), 7.50 (1H, s, Ar-H), 7.31 (1H, d, J = 8.3Hz, Ar-H), 7.16 (1H, d, J = 8.3Hz, Ar-H), 7.02 (1H, s, Ar-H), 4.61 (1H, br s, -NH-), 3.54 (2H, s, Ar-CH₂N-), 3.45 (2H, q, J = 6.2Hz, -CH₂NH-), 2.94 (2H, t, J = 6.2Hz, Ar-CH₂-), 2.27 (6H, s, -NMe₂), 1.43 (9H, s, t-Bu).

6. 3-[2-(N-Tert-butyloxycarbonylamino)ethyl]-5-trimethylammoniummethyl-1H-indole iodide

A solution of the product from step 5 (2.9g) in a mixture of anhydrous diethyl ether (170ml) and iodomethane (36ml) was allowed to stand at room temperature for 16 hours in the dark. The white solid was collected by filtration, washed with diethyl ether and dried over phosphorous pentoxide at 50 °C under vacuum to give 4.2g (100%) of the title compound; mp 199-202 °C (decomposition); δ_H (360MHz, DMSO-d₆) 11.09 (1H, br s, indole N-H), 7.69 (1H, s, Ar-H), 7.44 (1H, d, J = 8.3Hz, Ar-H), 7.26 (1H, s, Ar-H), 7.19 (1H, d, J = 8.3Hz, Ar-H), 6.89 (1H, br t, -NH-), 4.57 (2H, s, Ar-CH₂N-), 3.23 (2H, q, J = 7.6Hz, -CH₂NH-), 3.01 (9H, s, -N⁺Me₃), 2.83 (2H, t, J = 7.6Hz, Ar-CH₂-), 1.37 (9H, s, t-Bu); m/z (FAB) 332. (Found: C, 49.30; H, 6.55; N, 8.79. C₁₉H₃₀IN₃O₂ requires: C, 49.68; H, 6.58; N, 9.15%).

EXAMPLE 140 3-(2-Aminoethyl)-5-[(1,1-dioxo-5-methyl-1,2,5-thiadiazolidin-2-yl)methyl]-1H-indoleMETHOD A45 1. 3-[2-(N-Tert-butyloxycarbonylamino)ethyl]-5-[(1,1-dioxo-5-methyl-1,2,5-thiadiazolidin-2-yl)methyl]-1H-indole

To a solution of Intermediate I (815mg, 2.19mmol), triphenylphosphine (666mg, 2.54mmol) and 2-methyl-1,2,5-thiadiazolidine-1,1-dioxide (346mg, 2.54mmol) [V.P. Arya, K. Nagarajan, S.J. Shenoy, Indian J. Chem., 1982, 21B, 941] in anhydrous tetrahydrofuran (12ml) was added dropwise, under nitrogen, diethyl azodicarboxylate (400μl, 2.54mmol) over 18 minutes. After being stirred at room temperature for 3 hours, solvents were removed under vacuum and the remaining residue was purified by flash chromatography (silica gel, dichloromethane - methanol, 98:2; and hexane-ethyl acetate, 40:60) to give 460mg (51.5%) of the title compound as a colourless thick oil; δ_H (360MHz, CDCl₃) 8.09 (1H, br s, indole N-H), 7.54 (1H, s, Ar-H), 7.35 (1H, d, J = 8.4Hz, Ar-H), 7.22 (1H, dd, J = 8.4 and 1.5Hz, Ar-H), 7.06 (1H, s, Ar-H), 4.60 (1H, br s, -NH-), 4.30 (2H, s, Ar-CH₂N-), 3.44 (2H, m, -CH₂NH-), 3.25 (2H, dd, J = 8.2 and 7.0Hz, -CH₂-), 3.15 (2H, dd, J = 8.2 and 7.0Hz, -CH₂-), 2.94 (2H, t, J = 6.8Hz, Ar-CH₂CH₂N-) 2.79 (3H, s, -NMe), 1.43 (9H, s, t-Bu); m/z (El) 408 (M⁺).

2. 3-(2-Aminoethyl)-5-[(1,1-dioxo-5-methyl-1,2,5-thiadiazolidin-2-yl)methyl]-1H-indole

A solution of the product from Step 1 (880 mg) in 98% formic acid (20 ml) was allowed to stand at room temperature for 30 minutes. The solvent was then removed under vacuum (bath temperature 30 °C) and the residue was azeotroped with a mixture of toluene (30ml) and methanol (10ml) to give a pale brown thick oil. Flash chromatography of the crude mixture (silica gel, dichloromethane-methanol-ammonia, 80:20:2) gave 450 mg (67.8%) of the title compound as a colourless thick oil; δ_H (250MHz, CDCl₃) 8.15 (1H, br s, indole N-H), 7.57 (1H, s, Ar-H), 7.34 (1H, d, J = 8.4Hz, Ar-H), 7.21 (1H, dd, J = 8.4 and 1.6Hz, Ar-H), 7.06 (1H, d, J = 2.1Hz, Ar-H), 4.31 (2H, s, Ar-CH₂-N), 3.28-3.12 (4H, m, -NCH₂CH₂N-), 3.03 (2H, t, J = 6.0Hz, -CH₂-), 2.90 (2H, t, J = 6.0Hz, -CH₂-), 2.78 (3H, s, -NMe); m/z (Cl) 309 (M⁺ + 1).

METHOD B1. 5-Methyl-2-(4-nitrobenzyl)-1,2,5-thiadiazolidine-1,1-dioxide

To a stirred suspension of anhydrous potassium carbonate (14.49g, 104.8mmol) in anhydrous dimethyl-formamide (80 ml) was added dropwise over 4 minutes a solution of 2-methyl-1,2,5-thiadiazolidine-1,1-dioxide (14g, 102.8mmol) in anhydrous dimethylformamide (40 ml), under nitrogen. After 5 minutes, solid 4-nitrobenzyl bromide (22.43g, 103.8mmol) was added in one portion and stirring was continued at room temperature for 5 hours. Water (200ml) was added and products were extracted into ethyl acetate (3 x 150 ml). The combined organic phases were washed with brine (1 x 50 ml), dried (Na₂SO₄) and concentrated. The crude residue was crystallized from ethyl acetate - hexane (70:30) to give 18.31g (67%) of the title compound as pale yellow crystals. Purification of the mother liquors by flash chromatography (silica gel, hexane - ethyl acetate, 30:70) afforded a further 5.1g (18.2%) of required product; mp 105-107 °C; δ_H (250MHz, CDCl₃) 8.22 (2H, d, J = 8.7Hz, Ar-H), 7.57 (2H, d, J = 8.7Hz, Ar-H), 4.32 (2H, s, Ar-CH₂-), 3.36-3.21 (4H, m, N-CH₂CH₂-N), 2.80 (3H, s, -NMe); m/z (Cl) 270 (M⁺ - 1).

2. 2-(4-Aminobenzyl)-5-methyl-1,2,5-thiadiazolidine-1,1-dioxide. Hydrochloride

A suspension of the product from Step 1 (20g, 74.72mmol) in a mixture of absolute ethanol (300ml), ethyl acetate (150ml), 2N hydrochloric acid (39ml) and water (25ml), was hydrogenated at 30psi for 7 minutes over 10% palladium on carbon (2g). The catalyst was removed by filtration, washed with ethanol (2 x 30ml) and solvents were removed under vacuum. The remaining residue was azeotropically dried with absolute ethanol (1 x 150ml) and further dried at high vacuum to give 20.36g (99.5%) of the required title compound as a white solid. A sample recrystallised from absolute ethanol showed: mp 153-156 °C (white needles); δ_H (250MHz, DMSO-d₆) 7.42 (2H, d, J = 8.4Hz, Ar-H), 7.29 (2H, d, J = 8.4Hz, Ar-H), 4.15 (2H, s, Ar-CH₂-N), 3.27-3.17 (4H, m, N-CH₂CH₂-N), 2.62 (3H, s, -NMe); m/z (Cl) 240 (M⁺ - 1).

3. 4-[(1,1-Dioxo-5-methyl-1,2,5-thiadiazolidin-2-yl)methyl]-phenylhydrazine

To a cooled (-10 °C) and stirred suspension of the product from Step 2 (20g, 72.0mmol) in concentrated hydrochloric acid (100ml) and water (10ml) was added dropwise a solution of sodium nitrite (5.22g, 75.6mmol) in water (40ml) at such a rate as to maintain the temperature below -5 °C (ca 20 minutes). After a further 10 minutes, the mixture was quickly filtered to remove solids and the filtrate was added portionwise to a cooled (-15 °C) and stirred solution of tin (II) chloride dihydrate (81.2g, 360mmol) in concentrated hydrochloric acid (60ml) at such a rate as to maintain the temperature below -10 °C (ca 15 minutes). The mixture was allowed to warm to 0 °C and it was concentrated to 50% of the volume under vacuum. The remaining acid aqueous solution was basified with 10N potassium hydroxide (temperature maintained below 30 °C) and the resulting mixture was shaken with ethyl acetate (500ml) and filtered through Hyflo supercel filter aid. The organic phase was decanted off and the basic aqueous solution was extracted with ethyl acetate (3 x 250ml). The combined organic phases were washed with brine (1 x 100ml), dried (Na₂SO₄) and concentrated. Crystallization of the remaining residue from ethyl acetate followed by flash chromatography purification of the mother liquors (silica gel, ethyl acetate - methanol, 98:2; and dichloromethane-methanol, 95:5) gave 6.5g (35%) of the required title compound as a yellow solid; δ_H (250MHz, DMSO-d₆) 7.07 (2H, d, J = 8.5Hz, Ar-H), 6.74 (2H, d, J = 8.5Hz, Ar-H), 6.70 (1H, br s, -NH-), 3.94 (2H, s, Ar-CH₂-N), 3.91 (2H, br s, -NH₂), 3.23-3.05 (4H, m, N-CH₂CH₂-N), 2.60 (3H, s, -NMe); m/z (El) 256 (M⁺).

4. 3-(2-Aminoethyl)-5-[(1,1-dioxo-5-methyl-1,2,5-thiadiazolidin-2-yl)methyl]-1H-indole

To a stirred solution of the product from Step 3 (3.0g, 11.70mmol) in a mixture of absolute ethanol (100ml), water (15ml) and 2N hydrochloric acid (5.85mL, 11.70mmol) was added 4-chlorobutanal dimethylacetal (1.78g, 11.70mmol) and the resulting solution was refluxed for 2 hours. The solvent was removed under vacuum and the residue was azeotroped dried with absolute ethanol (50ml). The remaining residue was heated with absolute ethanol (100ml) and the solvent was decanted off from the dark residual solid. The solution was allowed to cool to room temperature and it was filtered again before solvents were removed under vacuum. Flash chromatography (silica gel, dichloromethane-methanol-ammonia, 90:10:1) of the residue gave 288mg (8%) of the title compound; the spectroscopic properties of this material were identical to those of the compound prepared using Method A.

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EXAMPLE 23-[2-(Dimethylamino)ethyl]-5-[(1,1-dioxo-5-methyl-1,2,5-thiadiazolidin-2-yl)methyl]-1H-indole. Succinate

15 To a cooled (-5 °C) and stirred solution of 3-(2-aminoethyl)-5-[(1,1-dioxo-5-methyl-1,2,5-thiadiazolidin-2-yl)methyl]-1H-indole (440mg, 1.42mmol) (Example 1) in methanol (20ml) and glacial acetic acid (0.4mL, 7.10mmol) was added sodium cyanoborohydride (196mg, 3.12mmol) followed by dropwise addition of a solution of formaldehyde (38% aqueous solution; 0.41ml) in methanol (5ml) over 5 minutes. The resulting solution was stirred at -5 °C for 20 minutes and at room temperature for 1 hour before saturated aqueous 20 potassium carbonate (19ml) was added and the methanol was removed under vacuum. The aqueous residue was diluted with water (5ml) and extracted with ethyl acetate (2 x 70ml), washed with brine (2 x 40ml), dried (MgSO_4) and concentrated. Flash chromatography of the crude product (silica gel, dichloromethane-methanol-ammonia, 90:10:1; and diethyl ether-methanol-ammonia, 70:30:1.6) afforded 25 376mg (78.8%) of the title compound free base as a colourless thick oil. The succinate salt was prepared and recrystallised from ethanol-diethyl ether; mp 178-181 °C; δ_{H} (360MHz, DMSO- d_6) 10.85 (1H, s, indole N-H), 7.51 (1H, s, Ar-H), 7.32 (1H, d, J = 8.3Hz, Ar-H), 7.18 (1H, d, J = 1.8Hz, Ar-H), 7.07 (1H, dd, J = 8.3 and 1.4Hz, Ar-H), 4.17 (2H, s, Ar-CH₂-N), 3.22 (2H, t, J = 6.1Hz, -CH₂-), 3.13 (2H, t, J = 6.1Hz, -CH₂-), 2.87 (2H, t, J = 6.9Hz, -CH₂-), 2.72 (2H, t, J = 6.9Hz, -CH₂), 2.63 (3H, s, -NMe), 2.38 (6H, s, -NMe₂), 2.31 (4H, s, succinic acid); m/z (Cl) 337 ($M^+ + 1$). (Found: C, 52.71; H, 6.92; N, 12.02. $C_{16}\text{H}_{24}\text{N}_4\text{O}_2\text{S} \times 1.0$ C₄H₆O₄ requires: C, 52.85; H, 6.65; N, 12.33%).

EXAMPLE 33-(2-Aminoethyl)-5-[2-(1,1-dioxo-5-methyl-1,2,5-thiadiazolidin-2-yl)ethyl]-1H-indole

35

1. 3-[2-(N-Tert-butyloxycarbonylamino)ethyl]-5-[2-(1,1-dioxo-5-methyl-1,2,5-thiadiazolidin-2-yl)ethyl]-1H-indole

The title compound was prepared from Intermediate 2 and 2-methyl-1,2,5-thiadiazolidine-1,1-dioxide by 40 a similar method to that described for Example 1 (Step 1) as a colourless thick oil; δ_{H} (250MHz, CDCl_3) 8.02 (1H, br s, indole N-H), 7.44 (1H, s, Ar-H), 7.30 (1H, d, J = 8.3Hz, Ar-H), 7.07 (1H, dd, J = 8.3 and 1.6Hz, Ar-H), 7.02 (1H, d, J = 2.2Hz, Ar-H), 4.61 (1H, br s, -NH-), 3.44 (2H, br q, J = 6.8Hz -CH₂-NH-), 3.36 (2H, dd, J = 8.3 and 5.7Hz, -CH₂N-), 3.29-3.24 (4H, m, -N CH₂CH₂N-), 3.05 (2H, dd, J = 8.3 and 5.7Hz, -CH₂), 2.93 (2H, t, J = 6.8Hz, Ar-CH₂CH₂NH-), 2.75 (3H, s, -NMe), 1.43 (9H, s, t-Bu); m/z (El) 422 (M^+). (Found: 45 m/z 422.1971. $C_{20}\text{N}_{30}\text{N}_4\text{O}_4\text{S}$ requires: m/z 422.1988).

2. 3-(2-Aminoethyl)-5-[2-(1,1-dioxo-5-methyl-1,2,5-thiadiazolidin-2-yl)ethyl]-1H-indole

A solution of the product from Step 1 (916mg) in anhydrous dichloromethane (15ml) and trifluoroacetic acid (4.5ml) was stirred at room temperature under a nitrogen atmosphere for 1 hour. Solvents were removed under vacuum and the residue was azeotroped with toluene-methanol. Flash chromatography of 50 the crude product (silica gel, dichloromethane-methanolammonia, 90:10:1) gave 372mg (59%) of the title compound as a colourless thick oil which solidified on standing; δ_{H} (250MHz, CDCl_3) 8.16 (1H, br s, indole N-H), 7.45 (1H, s, Ar-H), 7.28 (1H, d, J = 8.3Hz, Ar-H), 7.05 (1H, dd, J = 8.3 and 1.5Hz, Ar-H), 7.02 (1H, d, J = 1.8Hz, Ar-H), 3.35 (2H, dd, J = 9.8 and 7.1Hz, -CH₂N-), 3.26 (4H, s, -NCH₂CH₂N-), 3.08-2.99 (4H, m, -CH₂), 2.88 (2H, t, J = 6.2Hz, Ar-CH₂CH₂NH₂), 2.75 (3H, s, -NMe); m/z (Cl) 323 ($M^+ + 1$). (Found: m/z 55 323.1543. $C_{15}\text{H}_{23}\text{N}_4\text{O}_2\text{S}$ requires: m/z 323.1542).

EXAMPLE 4**3-[2-(Dimethylamino)ethyl]-5-[2-(1,1-dioxo-5-methyl-1,2,5-thiadiazolidin-2-yl)ethyl]-1H-indole. Oxalate**

5 The title compound was prepared in 81% yield from 3-(2-aminoethyl)-5-[2-(1,1-dioxo-5-methyl-1,2,5-thiadiazolidin-2-yl)ethyl]-1H-indole (Example 3) following the conditions described for Example 2. The oxalate salt was prepared and recrystallised from methanol-diethyl ether; mp 137-139°C; δ_H (360MHz, DMSO-d₆) 10.88 (1H, s, indole N-H), 7.45 (1H, s, Ar-H), 7.29 (1H, d, J = 8.2Hz, Ar-H), 7.20 (1H, s, Ar-H), 7.00 (1H, d, J = 8.2 Hz, Ar-H), 3.34-3.30 (2H, m, -CH₂-), 3.28-3.16 (6H, m, -CH₂-), 3.06-3.01 (2H, m, -CH₂-), 10. 2.95-2.90 (2H, m, -CH₂-), 2.79 (6H, s, -NMe₂), 2.60 (3H, s, -NMe); m/z (EI) 350 (M⁺). (Found: C, 51.51; H, 6.47; N, 12.53. C₁₇H₂₆N₄O₂S x 1.0 C₂H₂O₄ requires: C, 51.80; H, 6.41; N, 12.72%).

EXAMPLE 5**15 3-(2-Aminoethyl)-5-[(5-(4-acetylaminobenzyl)-1,1-dioxo-1,2,5-thiadiazolidin-2-yl)methyl]-1H-indole****1. 2-Tert-butyl-5-(4-nitrobenzyl)-1,2,5-thiadiazolidine-1,1-dioxide**

15 The title compound was prepared in 70% yield from 2-tert-butyl-1,2,5-thiadiazolidine-1,1-dioxide [M. Preiss, Chem. Ber., 1978, 111, 1915] and 4-nitrobenzyl bromide following the procedure described for Example 1 (Method B, Step 1); mp 113°C (ethyl acetate - hexane, 60:40); δ_H (360MHz, CDCl₃) 8.21 (2H, d, J = 8.7Hz, Ar-H), 7.58 (2H, d, J = 8.7Hz, Ar-H), 4.24 (2H, s, Ar-CH₂-), 3.40 (2H, t, J = 6.2Hz, -CH₂-), 3.17 (2H, t, J = 6.2Hz, -CH₂-), 1.44 (9H, s, t-Bu); m/z (EI) 313 (M⁺).

25 2. 2-(4-Nitrobenzyl)-1,2,5-thiadiazolidine-1,1-dioxide

30 A solution of the product from Step 1 (1.5g) in anhydrous dichloromethane (10ml) and trifluoroacetic acid (10ml) was allowed to stand at room temperature for 48 hours. Solvents were removed under vacuum and the remaining residue was azeotroped with methanol (1 x 25ml) and crystallised from ethyl acetate-hexane to give 966mg (78%) of the title compound as a pale yellow solid; mp 115-117°C; δ_H (250MHz, CDCl₃) 8.23 (2H, d, J = 8.8Hz, Ar-H), 7.57 (2H, d, J = 8.8Hz, Ar-H), 4.38 (1H, br t, -NH-), 4.29 (2H, s, Ar-CH₂-), 3.54 (2H, q, J = 6.6 Hz, -CH₂-NH-), 3.34 (2H, t, J = 6.6Hz, -CH₂-).

35 3. 3-[2-(N-Tert-butyloxycarbonylamino)ethyl]-5-[(1,1-dioxo-5-(4-nitrobenzyl)-1,2,5-thiadiazolidin-2-yl)methyl]-1H-indole

40 To a stirred solution of Intermediate 1 (920mg, 3.17mmol), 2-(4-nitrobenzyl)-1,2,5-thiadiazolidine-1,1-dioxide (900mg, 3.49mmol) and triphenylphosphine (914mg, 3.49mmol) in anhydrous tetrahydrofuran (25ml) was added dropwise over 13 minutes diethyl azodicarboxylate (549μL, 3.49mmol) under a nitrogen atmosphere. After being stirred at room temperature for 4.5 hours, solvents were removed under vacuum and the remaining residue was purified three times by flash chromatography (silica gel, dichloromethane-ethanol, 97:3; diethyl ether; and hexane - ethyl acetate, 40:60) to give 793mg (47.2%) of the title compound as a yellow foam; δ_H (250MHz, CDCl₃) 8.22 (2H, d, J = 8.8Hz, Ar-H), 8.10 (1H, br s, indole N-H), 7.58 (2H, d, J = 8.8Hz, Ar-H), 7.56 (1H, s, Ar-H), 7.36 (1H, d, J = 8.4Hz, Ar-H), 7.23 (1H, dd, J = 8.4 and 1.6Hz, Ar-H), 7.06 (1H, d, J = 2.1Hz, Ar-H), 4.61 (1H, br s, -NH-), 4.35 (2H, s, Ar-CH₂-), 4.34 (2H, s, Ar-CH₂-), 3.45 (2H, br q, J = 6.9Hz, -CH₂NH-), 3.19 (4H, s, -NCH₂CH₂N-), 2.95 (2H, t, J = 6.9Hz, Ar-CH₂CH₂NH-), 1.43 (9H, s, t-Bu).

50 4. 4. 3-[2-(N-Tert-butyloxycarbonylamino)ethyl]-5-[(5-(4-acetylaminobenzyl)-1,1-dioxo-1,2,5-thiadiazolidin-2-yl)methyl]-1H-indole

55 A solution of the product from Step 3 (780mg, 1.47mmol) in a mixture of absolute ethanol (30ml) and 2N hydrochloric acid (0.74ml) was hydrogenated over palladium on carbon (10%; 108mg) at 30 psi for 10 minutes. The catalyst was removed by filtration, washed with absolute ethanol (2 x 10ml) and solvents were removed under vacuum. The remaining residue, after being azeotroped with a mixture of toluene (30ml) and methanol (10ml), was dissolved in anhydrous dichloromethane (20ml) and treated with anhydrous triethylamine (0.61ml, 4.41mmol) followed by acetic anhydride (0.20mL, 2.20mmol). After being stirred at room temperature for 1.5 hours, 1N hydrochloric acid (30ml) was added and the products were extracted

into ethyl acetate (2 x 75ml). The combined organic extracts were washed with brine (1 x 40ml), dried (MgSO_4) and concentrated. Flash chromatography of the residue (silica gel, hexane - ethyl acetate, 20:80) gave 684mg (86%) of the title compound as a white foam; δ_{H} (250MHz, CDCl_3) 8.12 (1H, br s, indole N-H), 7.54 (1H, s, Ar-H), 7.49 (2H, d, J = 8.4Hz, Ar-H), 7.38 (1H, br s, Ar-NHCO-), 7.34 (1H, d, J = 8.2Hz, Ar-H), 5 7.33 (2H, d, J = 8.4Hz, Ar-H), 7.21 (1H, dd, J = 8.2 and 1.6 Hz, Ar-H), 7.05 (1H, d, J = 2.2Hz, Ar-H), (1H, br s, -NH-), 4.31 (2H, s, Ar- CH_2 -), 4.20 (2H, s, Ar- CH_2 -), 3.45 (2H, br q, J = 6.8Hz, - CH_2NH -), 3.11 (4H, m, - $\text{NCH}_2\text{CH}_2\text{N}$ -), 2.94 (2H, t, J = 6.8Hz, Ar- $\text{CH}_2\text{CH}_2\text{NH}$ -), 2.17 (3H, s, CH_3CO -), 1.43 (9H, s, t-Bu).

5. 3-(2-Aminoethyl)-5-[(5-(4-acetylaminobenzyl-1,1-dioxo-1,2,5-thiadiazolidin-2-yl)methyl]-1H-indole

10 The title compound was prepared in 67% yield from 3-[2-(N-tert-butyloxycarbonylamino)ethyl]-5-[5-(4-acetylaminobenzyl-1,1-dioxo-1,2,5-thiadiazolidin-2-yl)methyl]-1H-indole (Step 4) by a similar method to that described in Example 1 (Step 2) as a white foam; δ_{H} (360MHz, CDCl_3), 8.14 (1H, br s, indole N-H), 7.56 (1H, s, Ar-H), 7.48 (2H, d, J = 8.4Hz, Ar-H), 7.46 (1H, br s, Ar-NHCO-), 7.33 (3H, d, J = 8Hz, Ar-H), 7.20 (1H, dd, J = 8.3 and 1.5Hz, Ar-H), 7.05 (1H, d, J = 2.1Hz, Ar-H), 4.31 (2H, s, Ar- CH_2 -), 4.20 (2H, s, Ar- CH_2 -), 3.10 (4H, s, - $\text{NCH}_2\text{CH}_2\text{N}$ -), 3.03 (2H, t, J = 6.4Hz, - CH_2 -), 2.90 (2H, t, J = 6.4Hz, - CH_2 -), 2.17 (3H, s, CH_3CO -).

EXAMPLE 6

3-[2-(Dimethylamino)ethyl]-5-[(5-(4-acetylaminobenzyl-1,1-dioxo-1,2,5-thiadiazolidin-2-yl)methyl]-1H-indole. Succinate

25 The title compound free base was prepared in 78% yield from 3-(2-aminoethyl)-5-[5-(4-acetylaminobenzyl-1,1-dioxo-1,2,5-thiadiazolidin-2-yl)methyl]-1H-indole (Example 5) following the conditions described for Example 2. The crude product was purified by flash chromatography (silica gel, dichloromethane-methanol-ammonia, 90:10:1.2) and the succinate salt was prepared and recrystallised from ethanol:diethyl ether; mp 158-161 °C, δ_{H} (360MHz, DMSO-d_6) 10.86 (1H, s, indole N-H), 9.94 (1H, s Ar-NHCO-), 7.55 (2H, d, J = 8.5Hz, Ar-H), 7.52 (1H, s, Ar-H), 7.32 (1H, d, J = 8.3Hz, Ar-H), 7.28 (2H, d, J = 8.5Hz, Ar-H), 7.18 (1H, s, Ar-H), 7.07 (1H, dd, J = 8.3 and 1.5Hz, Ar-H), 4.18 (2H, s, Ar- CH_2 -), 4.07 (2H, s, Ar- CH_2 -), 3.12 (4H, s, - $\text{NCH}_2\text{CH}_2\text{N}$ -), 2.87 (2H, br t, J = 8Hz, - CH_2 -), 2.73 (2H, br t, J = 8Hz, - CH_2 -), 2.38 (6H, s, - NMe_2), 2.36 (4H, s, succinic acid), 2.03 (3H, s, CH_3CO -).

30 Examples 7 and 8 were prepared from Intermediate 1 and the appropriate 1,2,5-thiadiazolidine-1,1-dioxide [V.P. Arya, K. Nagarajan, S.J. Shenoy, Indian J. Chem., 1982, 21B, 941; M. Preiss, Chem. Ber., 1978, 111, 1915] using a similar method to that described for Example 1 (Method A).

EXAMPLE 7

3-(2-Aminoethyl)-5-[(1,1-dioxo-1,2,5-thiadiazolidin-2-yl)methyl]-1H-indole

1. 3-[2-(N-Tert-butyloxycarbonylamino)ethyl]-5-[(1,1-dioxo-1,2,5-thiadiazolidin-2-yl)methyl]-1H-indole

40 White foam; δ_{H} (250MHz, CDCl_3) 8.11 (1H, br s, indole N-H), 7.57 (1H, s, Ar-H), 7.35 (1H, d, J = 8.3Hz, Ar-H), 7.21 (1H, dd, J = 8.3 and 1.5Hz, Ar-H), 7.08 (1H, d, J = 2.2Hz, Ar-H), 4.62 (1H, br s, -NH-), 4.43 (1H, br s, -NH-), 4.29 (2H, s, Ar- CH_2N -), 3.44 (4H, br q, - CH_2NHBOC and - CH_2 -), 3.27 (2H, t, J = 6.8Hz, - CH_2 -), 2.94 (2H, t, J = 6.9Hz, Ar- $\text{CH}_2\text{CH}_2\text{N}$ -), 1.43 (9H, s, t-Bu); m/z (EI) 394 (M^+). (Found: m/z 394.1644. $C_{18}\text{H}_{26}\text{N}_4\text{O}_4\text{S}$ requires: m/z 394.1675).

2. 3-(2-Aminoethyl)-5-[(1,1-dioxo-1,2,5-thiadiazolidin-2-yl)methyl]-1H-indole

50 Colourless thick oil; δ_{H} (250MHz, CDCl_3 - CD_3OD) 7.54 (1H, s, Ar-H), 7.33 (1H, d, J = 8.4Hz, Ar-H), 7.15 (1H, dd, J = 8.4 and 1.6Hz, Ar-H), 7.05 (1H, s, Ar-H), 4.24 (2H, s, Ar- CH_2N -), 3.43-3.39 (2H, m, - CH_2 -), 3.25-3.19 (2H, m, - CH_2 -), 3.00-2.85 (4H, m, Ar- $\text{CH}_2\text{CH}_2\text{N}$ -).

EXAMPLE 8

3-(2-Aminoethyl)-5-[(1,1-dioxo-5-isopropyl-1,2,5-thiadiazolidin-2-yl)methyl]-1H-indole

1. 3-[2-(N-Tert-butyloxycarbonylamino)ethyl]-5-[(1,1-dioxo-5-isopropyl-1,2,5-thiadiazolidin-2-yl)methyl]-1H-indole

Colourless thick oil; δ_H (250MHz, CDCl₃) 8.14 (1H, br s, indole N-H), 7.54 (1H, s, Ar-H), 7.33 (1H, d, J = 8.3Hz, Ar-H), 7.21 (1H, dd, J = 8.3 and 1.6Hz, Ar-H), 7.04 (1H, d, J = 2.2Hz, Ar-H), 4.61 (1H, br s, -NH-), 4.26 (2H, s, Ar-CH₂N-), 3.77 (1H, m, 6.6Hz, -CH-), 3.44 (2H, br q, -CH₂NH-), 3.28-3.23 (2H, m, -CH₂-), 3.16-3.10 (2H, m, -CH₂-), 2.94 (2H, t, J = 6.9Hz, Ar-CH₂CH₂N-), 1.43 (9H, s, t-Bu), 1.29 (6H, d, J = 6.6Hz, Me₂CH-); m/z (EI) 437 (M⁺ + 1).

10 2. 3-(2-Aminoethyl)-5-[(1,1-dioxo-5-isopropyl-1,2,5-thiadiazolidin-2-yl)methyl]-1H-indole

Colourless thick oil; δ_H (360MHz, CDCl₃) 8.25 (1H, br s, indole N-H), 7.55 (1H, s, Ar-H), 7.32 (1H, d, J = 8.3Hz, Ar-H), 7.18 (1H, br d, J = 8.3Hz, Ar-H), 7.05 (1H, s, Ar-H), 4.25 (2H, s, Ar-CH₂N-), 3.73 (1H, m, J = 6.6Hz, -CH-), 3.24 (2H, t, J = 6.4Hz, -CH₂-), 3.13 (2H, t, J = 6.4Hz, -CH₂-), 3.02 (2H, m, -CH₂-), 2.90 (2H, m, -CH₂-), 1.29 (6H, d, J = 6.6Hz, Me₂CH-); m/z (CI) 337 (M⁺ + 1).

Examples 9 and 10 were prepared from Intermediate 2 and the appropriate 1,2,5-thiadiazolidine-1,1-dioxide following the procedure described for Example 1 (Method A).

EXAMPLE 9

20

3-(2-Aminoethyl)-5-[2-(1,1-dioxo-1,2,5-thiadiazolidin-2-yl)ethyl]-1H-indole

1. 3-[2-(N-Tert-butyloxycarbonylamino)ethyl]-5-[2-(1,1-dioxo-1,2,5-thiadiazolidin-2-yl)ethyl]-1H-indole

25 The title compound was isolated in 5% yield as a white solid; δ_H (250MHz, CDCl₃) 8.00 (1H, br s, indole N-H), 7.53 (1H, s, Ar-H), 7.30 (1H, d, J = 8.3Hz, Ar-H), 7.06 (1H, dd, J = 8.3 and 1.5Hz, Ar-H), 7.02 (1H, d, J = 2.2Hz, Ar-H), 4.62 (2H, br s, -NH-), 3.50-3.30 (4H, m, -CH₂-), 3.07 (2H, t, J = 8.2Hz, -CH₂-), 2.94 (2H, t, J = 6.8Hz, Ar-CH₂CH₂NH-), 1.43 (9H, s, t-Bu).

30

2. 3-(2-Aminoethyl)-5-[2-(1,1-dioxo-1,2,5-thiadiazolidin-2-yl)ethyl]-1H-indole

White solid; δ_H (360MHz, DMSO-d₆) 7.37 (1H, s, Ar-H), 7.25 (1H, d, J = 8.3Hz, Ar-H), 7.08 (1H, d, J = 2.0Hz, Ar-H), 6.95 (1H, dd, J = 8.3 and 1.4Hz, Ar-H), 3.27 (4H, m, -CH₂-), 3.10 (2H, t, J = 8.3Hz, -CH₂-), 2.90 (2H, t, J = 8.3Hz, -CH₂-), 2.60 (2H, m, -CH₂-), 2.71 (2H, m, -CH₂-); m/z (CI) 309 (M⁺ + 1).

35

EXAMPLE 10

3-(2-Aminoethyl)-5-[2-(1,1-dioxo-5-ethyl-1,2,5-thiadiazolidin-2-yl)ethyl]-1H-indole

40 **1. 3-[2-(N-Tert-butyloxycarbonylamino)ethyl]-5-[2-(1,1-dioxo-5-ethyl-1,2,5-thiadiazolidin-2-yl)ethyl]-1H-indole**

The title compound was isolated in 56% yield as a white solid; δ_H (360MHz, CDCl₃) 8.00 (1H, br s, indole N-H), 7.44 (1H, s, Ar-H), 7.30 (1H, d, J = 8.3Hz, Ar-H), 7.07 (1H, dd, J = 8.3 and 1.4Hz, Ar-H), 7.02 (1H, s, Ar-H), 4.62 (1H, br s, -NH-), 3.45 (2H, m, -CH₂NH-), 3.33 (2H, dd, J = 8.5 and 5.8Hz, -CH₂N-), 3.27 (4H, s, -NCH₂CH₂N-), 3.11 (2H, q, J = 7.3Hz, CH₃CH₂N-), 3.05 (2H, dd, J = 8.5 and 5.8Hz, -CH₂-), 2.93 (2H, t, J = 6.8Hz, Ar-CH₂CH₂NH-), 1.43 (9H, s, t-Bu), 1.26 (3H, t, J = 7.3Hz, -CH₃).

2. 3-(2-Aminoethyl)-5-[2-(1,1-dioxo-5-ethyl-1,2,5-thiadiazolidin-2-yl)ethyl]-1H-indole

50 White solid; δ_H (360MHz, CDCl₃) 8.07 (1H, br s, indole N-H), 7.45 (1H, s, Ar-H), 7.28 (1H, d, J = 8.3Hz, Ar-H), 7.05 (1H, dd, J = 8.3 and 1.4Hz, Ar-H), 7.04 (1H, s, Ar-H), 3.36-3.24 (6H, m, -CH₂-), 3.13-3.02 (6H, m, -CH₂-), 2.93 (2H, t, J = 6.4Hz, -CH₂-), 1.26 (3H, t, J = 7.3Hz, -CH₃).

Examples 11-14 were prepared from the products of Examples 7-10 using a similar method to that described for Example 2.

55

EXAMPLE 11

3-[2-(Dimethylamino)ethyl]-5-[(1,1-dioxo-1,2,5-thiadiazolidin-2-yl)methyl]-1H-indole. Succinate

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The succinate salt was prepared and recrystallized from ethanol-diethyl ether; mp 159-161 °C; δ_H - (360MHz, DMSO-d₆) 10.85 (1H, s, indole N-H), 7.49 (1H, s, Ar-H), 7.31 (1H, d, J = 8.4Hz, Ar-H), 7.10 (2H, br s, Ar-H and -NH-), 7.06 (1H, dd, J = 8.4 and 1.5Hz, Ar-H), 4.09 (2H, s, Ar-CH₂N-), 3.24 (2H, br q, J = 6.5Hz, -CH₂NH-), 3.15 (2H, t, J = 6.5Hz, -HNCH₂CH₂N-), 2.87 (2H, br t, J = 8.4Hz, -CH₂-), 2.73 (2H, br t, J = 8.4Hz, -CH₂-), 2.38 (6H, s, -NMe₂), 2.36 (4H, s, succinic acid); m/z (Cl) 323 (M⁺ + 1). (Found: C, 52.05; H, 6.10; N, 12.40. C₁₅H₂₂N₄O₂S x 1.0 C₄H₆O₄ requires: C, 51.80; H, 6.41; N, 12.72%).

EXAMPLE 12

10 **3-[2-(Dimethylamino)ethyl]-5-[(1,1-dioxo-5-isopropyl-1,2,5-thiadiazolidin-2-yl)methyl]-1H-indole. Oxalate**

The oxalate salt was prepared and recrystallised from ethanol-diethyl ether; mp 186-187 °C; δ_H - (360MHz, DMSO-d₆) 11.00 (1H, s, indole N-H), 7.56 (1H, s, Ar-H), 7.36 (1H, d, J = 8.3Hz, Ar-H), 7.25 (1H, s, Ar-H), 7.10 (1H, d, J = 8.3Hz, Ar-H), 4.12 (2H, s, Ar-CH₂N-), 3.54 (1H, m, J = 6.6Hz, -CH-), 3.29-3.21 (4H, m, -CH₂-), 3.12-3.00 (4H, m, -CH₂-), 2.80 (6H, s, -NMe₂), 1.19 (6H, d, J = 6.6Hz, Me₂CH-); m/z (El) 364 (M⁺). (Found: C, 52.59; H, 6.55; N, 12.23. C₁₈H₂₈N₄O₂S x 1.0 C₂H₂O₄ requires: C, 52.85; H, 6.65; N, 12.33%).

EXAMPLE 13

20 **3-[2-(Dimethylamino)ethyl]-5-[2-(1,1-dioxo-1,2,5-thiadiazolidin-2-yl)ethyl]-1H-indole. Oxalate**

The oxalate salt was prepared and recrystallised from ethanol-diethyl ether; mp 154-155 °C; δ_H - (360MHz, D₂O) 7.57 (1H, s, Ar-H), 7.48 (1H, d, J = 8.4Hz, Ar-H), 7.32 (1H, s, Ar-H), 7.19 (1H, dd, J = 8.4 and 1.3Hz, Ar-H), 3.50-3.42 (6H, m, -CH₂-), 3.37 (2H, t, J = 7.0Hz, -CH₂-), 3.23 (2H, t, J = 7.3Hz, -CH₂-), 3.05 (2H, t, J = 7.0Hz, -CH₂-), 2.90 (6H, s, -NMe₂); m/z (Cl) 337 (M⁺ + 1). (Found: C, 50.60; H, 5.79; N, 12.78. C₁₆H₂₄N₄O₂S x 1.0 C₂H₂O₄ requires: C, 50.69; H, 6.15; N, 13.14%).

EXAMPLE 14

30 **3-[2-(Dimethylamino)ethyl]-5-[2-(1,1-dioxo-5-ethyl-1,2,5-thiadiazolidin-2-yl)ethyl]-1H-indole. Succinate**

The succinate salt was prepared and recrystallised from ethanol-diethyl ether; mp 144-145 °C; δ_H - (360MHz, D₂O) 7.57 (1H, s, Ar-H), 7.49 (1H, d, J = 8.4Hz, Ar-H), 7.33 (1H, s, Ar-H), 7.19 (1H, dd, J = 8.4 and 1.4Hz, Ar-H), 3.49 (2H, t, J = 7.3Hz, -CH₂-), 3.42-3.31 (6H, m, -CH₂-), 3.24 (2H, t, J = 7.3Hz, -CH₂-), 3.10-3.03 (4H, m, -CH₂-), 2.91 (6H, s, -NMe₂), 2.52 (4H, s, succinic acid), 1.20 (3H, t, J = 7.3Hz, CH₃-); m/z (El) 364 (M⁺). (Found: C, 53.99; H, 6.95; N, 11.23. C₁₈H₂₈N₄O₂S x 1.0 C₄H₆O₄ x 0.3H₂O requires: C, 54.15; H, 7.15; N, 11.48%).

40 **EXAMPLE 15**

3-[2-(Methylamino)ethyl]-5-[(1,1-dioxo-5-methyl-1,2,5-thiadiazolidin-2-yl)methyl]-1H-indole. Succinate.

1. **3-[2-(N-Formylamino)ethyl]-5-hydroxymethyl-1H-indole**

To a cooled(-70 °C) and stirred solution of ethyl 3-[2-(N-tert-butyloxycarbonylamino)ethyl]-1H-indole-5-carboxylate (Intermediate 1, step 3) (5.2g, 15.8mmol) in anhydrous tetrahydrofuran (250ml) was added dropwise, under nitrogen, diisobutylaluminium hydride (1M in toluene; 65.7ml) over 15 minutes. The mixture was then allowed to warm to 0 °C and it was stirred for 2 hours before the excess of diisobutylaluminium hydride was destroyed by dropwise addition of anhydrous methanol (25ml) at -50 °C. Aqueous citric acid (10%; 200ml) was added, the mixture was diluted with ethyl acetate (200ml) and the organic phase was decanted off, washed with brine (50ml), dried (MgSO₄) and concentrated. Flash chromatography (silica gel, dichloromethane-methanol 96:4 to 90:10) of the residue gave 2.1g of Intermediate 1 and 0.8g of the title compound as a colourless thick oil; δ_H (360MHz, DMSO-d₆) 10.73 (1H, s, indole N-H), 8.05 (1H, br s -NHCHO), 8.02 (1H, s, -NCHO), 7.46 (1H, s, Ar-H), 7.27 (1H, d, J = 8.3Hz, Ar-H), 7.13 (1H, d, J = 2.1Hz, Ar-H), 7.04 (1H, dd, J = 8.3 and 1.4Hz, Ar-H), 4.95 (1H, t, J = 5.6Hz, -OH), 4.54 (2H, d, J = 5.6Hz, Ar-CH₂OH), 3.37 (2H, q, J = 7.4Hz, -CH₂N-), 2.82 (2H, t, J = 7.4Hz, Ar-CH₂-); m/z (El) 218 (M⁺).

2. 3-[2-(N-Formylamino)ethyl]-5-[(1,1-dioxo-5-methyl-1,2,5-thiadiazolidin-2-yl)methyl]-1H-indole

To a cooled (0 °C) and stirred solution of the product from step 1 (780mg, 3.57mmol), triphenylphosphine (1.13g, 4.29mmol) and 2-methyl-1,2,5-thiadiazolidine-1,1-dioxide (584mg, 4.29mmol) in anhydrous tetrahydrofuran (20ml) was added dropwise, under nitrogen, diethyl azodicarboxylate (675µl, 4.29mmol) over 8 minutes. The mixture was allowed to warm to room temperature and it was stirred for 2 hours before anhydrous dimethylformamide (2ml) was added and stirring was continued for a further 16 hours. Solvents were removed under vacuum and the residue was purified by flash chromatography (silica gel, dichloromethane-methanol 95:5; and ethyl acetate-methanol 99:1) to give 420mg (40.8%) of the title compound as a colourless thick oil; δ_H (250MHz, CDCl₃) 8.30 (1H, br s, indole N-H), 8.11 (1H, s, NCHO), 7.56 (1H, s, Ar-H), 7.34 (1H, d, J = 8.4Hz, Ar-H), 7.19 (1H, dd, J = 8.4 and 1.6Hz, Ar-H); 7.05 (1H, d, J = 2.4Hz, Ar-H), 5.77 (1H, br s, -NH-), 4.30 (2H, s, Ar-CH₂N-), 3.62 (2H, q, J = 6.6Hz, CH₂NH-), 3.28-3.16 (4H, m, -CH₂-), 2.98 (2H, t, J = 6.6Hz, Ar-CH₂-), 2.77 (3H, s, -NMe).

15 3. 3-[2-(Methylamino)ethyl]-5-[(1,1-dioxo-5-methyl-1,2,5-thiadiazolidin-2-yl)methyl]-1H-indole. Succinate

To a cooled (0 °C) and stirred solution of the product from step 2 (440mg, 1.31mmol) in anhydrous tetrahydrofuran (10ml) was added dropwise, under nitrogen, borane tetrahydrofuran complex (1M in tetrahydrofuran; 3.9ml) over 3 minutes. The mixture was allowed to warm to room temperature and it was stirred for 6 hours before the excess of borane was destroyed by dropwise addition of methanol (4ml). Solvents were removed under vacuum and the residue was dissolved in a mixture of 2N hydrochloric acid (25ml) and methanol (25ml) and it was allowed to stand at 30 °C for 20 minutes. The mixture was then basified with 2N aqueous sodium hydroxide (40ml), the methanol was removed under vacuum and products were extracted with ethyl acetate (2 x 100ml). The combined organic extracts were washed with brine (1 x 40ml), dried (Na₂SO₄) and concentrated. Flash chromatography of the residue (silica gel, diethyl ether-methanol-ammonia 70:30:2.1) gave 100mg (26%) of the required title compound free base as a thick oil. The succinate salt was prepared and recrystallised from ethanol-diethyl ether; mp 140-142 °C; δ_p (360MHz, DMSO-d₆) 10.95 (1H, br s, indole N-H), 7.53 (1H, s, Ar-H), 7.35 (1H, d, J = 8.3Hz, Ar-H), 7.23 (1H, s, Ar-H), 7.09 (1H, d, J = 8.3Hz, Ar-H), 4.17 (2H, s, Ar-CH₂N-), 3.24-3.20 (2H, m, -CH₂-), 3.16-3.12 (2H, m, -CH₂-), 3.06 (2H, t, J = 7.6Hz, -CH₂-), 2.95 (2H, t, J = 7.6Hz, -CH₂-), 2.62 (3H, s, -NMe), 2.53 (3H, s, -NHMe), 2.27 (4H, s, succinic acid); m/z (CI) 323 (M⁺ + 1). (Found: C, 51.84; H, 6.19; N, 12.52. C₁₅H₂₂N₄O₂S x 1.0 C₄H₆O₄ requires: C, 51.80; H, 6.41; N, 12.72%).

EXAMPLE 163-(2-Aminoethyl)-5-[(1,1-dioxo-6-methyl-3,4,5,6-tetrahydro-1,2,6-thiadiazin-2-yl)methyl]-1H-indole1. 3-[2-(N-Tert-butyloxycarbonylamino)ethyl]-5-[(1,1-dioxo-1,2,6-thiadiazin-2-yl)methyl]-1H-indole

The title compound was prepared in 38% isolated yield from Intermediate 1 and 1,2,6-thiadiazine-1,1-dioxide (J. Org. Chem., 1982, 47, 536) using a similar method to that described for Example 1 (Method A, step 1). White foam; δ_H (250MHz, CDCl₃) 8.20 (1H, br s, indole N-H), 7.90 (1H, dd, J = 4.5 and 2.5Hz, -CH-), 7.60 (1H, s, Ar-H), 7.40 (1H, d, J = 8.5Hz, Ar-H), 7.22 (1H, dd, J = 8.5 and 1.7Hz, Ar-H), 7.13 (1H, dd, J = 7.3 and 2.5Hz, -CH-), 7.10 (1H, d, J = 2.1Hz, Ar-H), 5.73 (1H, dd, J = 7.3 and 4.5Hz, -CH-), 5.05 (2H, s, Ar-CH₂N-), 4.60 (1H, br s, -NH-), 3.44 (2H, m, Ar-CH₂CH₂N-), 2.95 (2H, t, J = 7.0Hz, Ar-CH₂-), 1.43 (9H, s, t-Bu); m/z (FAB) 405 (M⁺ + 1).

2. 3-[2-(N-Tert-butyloxycarbonylamino)ethyl]-5-[(1,1-dioxo-6-methyl-3,4,5,6-tetrahydro-1,2,6-thiadiazin-2-yl)methyl]-1H-indole.

To a stirred solution of 2-methyl-3,4,5,6-tetrahydro-1,2,6-thiadiazine-1,1-dioxide (300mg, 2.0mmol) in anhydrous dimethylformamide (10ml) was added sodium hydride (60% dispersion in oil; 71mg) and the mixture was stirred under nitrogen for 20 minutes. A solution of the product from step 1 (300mg, 0.74mmol) in anhydrous dimethylformamide (5ml) was added dropwise via cannula over 5 minutes to the above solution and the mixture was heated at 90-100 °C for 45 minutes. After being cooled to room temperature, the mixture was diluted with water (50ml) and extracted with ethyl acetate (2 x 100ml). The combined organic solutions were washed with brine (1 x 50ml), dried (MgSO₄) and concentrated. Flash chromatography (silica gel, diethyl ether) of the residue gave 100mg (32%) of the required title compound; δ_H -

(250MHz, CDCl₃) 8.15 (1H, br s, indole N-H), 7.51 (1H, s, Ar-H), 7.35 (1H, d, J = 8.5Hz, Ar-H), 7.21 (1H, dd, J = 8.5 and 1.5Hz, Ar-H), 7.05 (1H, d, J = 2.1Hz, Ar-H), 4.60 (1H, br s, -NH-), 4.36 (2H, s, Ar-CH₂N-), 3.45 (2H, br q, J = 6.9Hz, -CH₂NH-), 3.38 (2H, t, J = 5.7Hz, -CH₂N-), 3.26 (2H, t, J = 5.8Hz, -CH₂N-), 2.94 (2H, t, J = 6.8Hz, ArCH₂CH₂NH-), 2.86 (3H, s, -NMe), 1.80-1.70 (2H, m, -CH₂-), 1.43 (9H, s, t-Bu).

5

3. 3-(2-Aminoethyl)-5-[(1,1-dioxo-6-methyl-3,4,5,6-tetrahydro-1,2,6-thiadiazin-2-yl)methyl]-1H-indole

To a stirred solution of the product from step 2 (95mg, 0.225mmol) in anhydrous dichloromethane (5ml) was added dropwise, under nitrogen, iodotrimethylsilane (35μl). After being stirred at room temperature for 10 12 minutes the reaction was quenched with methanol (1ml), solvents were removed under vacuum and the residue was purified by flash chromatography (silica gel, dichloromethane-methanol-ammonia 80:20:2) to give 44mg (61%) of the title compound; δ_H (250MHz, CDCl₃) 8.21 (1H, br s, indole N-H), 7.52 (1H, s, Ar-H), 7.33 (1H, d, J = 8.3Hz, Ar-H), 7.18 (1H, d, J = 8.3Hz, Ar-H), 7.05 (1H, br s, Ar-H), 4.35 (2H, s, Ar-CH₂N-), 3.37 (2H, t, J = 5.8Hz, -CH₂N-), 3.25 (2H, t, J = 5.6Hz, -CH₂N-), 3.02 (2H, m, -CH₂-), 2.91 (2H, m, ArCH₂CH₂NH₂), 2.85 (3H, s, -NMe), 1.74 (2H, m, -CH₂-); m/z (Cl) 323 (M⁺ + 1).

EXAMPLE 17

3-[2-(Dimethylamino)ethyl]-5-[(1,1-dioxo-6-methyl-3,4,5,6-tetrahydro-1,2,6-thiadiazin-2-yl)methyl]-1H-indole.
Oxalate

The title compound was prepared in 77% yield from 3-(2-aminoethyl)-5-[(1,1-dioxo-6-methyl-3,4,5,6-tetrahydro-1,2,6-thiadiazin-2-yl)methyl]-1H-indole (Example 16) following the conditions described for Example 2. The oxalate salt was prepared and recrystallised from ethanol-diethyl ether; mp 190-191 °C; δ_H (360MHz, D₂O) 7.64 (1H, s, Ar-H), 7.52 (1H, d, J = 8.4Hz, Ar-H), 7.35 (1H, s, Ar-H), 7.27 (1H, dd, J = 8.4 and 1.5Hz, Ar-H), 4.38 (2H, s, Ar-CH₂N-), 3.48 (2H, t, J = 7.3Hz, -CH₂NMe₂), 3.42 (2H, t, J = 5.9Hz, -CH₂N-), 3.33 (2H, t, J = 5.7Hz, -CH₂N-), 3.24 (2H, t, J = 7.3Hz, Ar-CH₂CH₂N-), 2.91 (6H, s, -NMe₂), 2.84 (3H, s, -NMe), 1.84 (2H, qn, J = 5.8Hz, -CH₂-); m/z (El) 350 (M⁺). (Found: C, 51.80; H, 6.20; N, 12.06. C₁₇H₂₆N₄O₂S x 1.05 C₂H₂O₄ x 0.2 C₂H₆O requires: C, 51.56; H, 6.50; N, 12.33%).

30

EXAMPLE 18

3-(2-Aminoethyl)-5-[(4,4-dimethyl-1,1-dioxo-1,2,5-thiadiazolidin-2-yl)methyl]-1H-indole

1. 3,3-Dimethyl-1,2,5-thiadiazolidine-1,1-dioxide

To a refluxing solution of sulfamide (27.25g, 283mmol) in anhydrous pyridine (300ml) was added dropwise 1,2-diamino-2-methylpropane (25g, 283mmol) over 2 hours. The resulting mixture was refluxed for further 16 hours under nitrogen before the solvent was removed under vacuum. The residue was triturated 40 with hexane and the solid was collected by filtration and purified by flash chromatography (silica gel, dichloromethane-methanol 96:4) to give 36.1g (85%) of the title compound as a white solid; mp 80-83 °C; δ_H (360MHz, DMSO-d₆) 7.08 (1H, br t, -NH-), 6.77 (1H, s, -NH-), 3.04 (2H, d, J = 6.9Hz, -CH₂-), 1.24 (6H, s, -CMe₂); m/z (El) 151 (M⁺ + 1).

2. 3-[2-(N-Tert-butyloxycarbonylamino)ethyl]-5-[(4,4-dimethyl-1,1-dioxo-1,2,5-thiadiazolidin-2-yl)methyl]-1H-indole

To a stirred solution of 3,3-dimethyl-1,2,5-thiadiazolidine-1,1-dioxide (360mg, 2.4mmol) in anhydrous dimethylformamide (10ml) was added sodium hydride (60% dispersion in oil; 87mg) and the mixture was stirred at room temperature for 30 minutes under nitrogen. A solution of Intermediate 3 (500mg, 1.09mmol) in anhydrous dimethylformamide (5ml) was added to the above mixture and it was heated at 100 °C for 40 minutes. Solvents were removed under vacuum, the residue was diluted with water (50ml) and products were extracted with diethyl ether (2x 75ml). The combined organic phases were washed with brine (1 x 40ml), dried (MgSO₄) and concentrated. Flash chromatography of the residue (silica gel, diethyl ether) gave 55 334mg (73%) of the required title compound; δ_H (250MHz, CDCl₃) 8.07 (1H, br s, indole N-H), 7.55 (1H, s, Ar-H), 7.36 (1H, d, J = 8.3Hz, Ar-H), 7.22 (1H, dd, J = 8.3 and 1.4Hz, Ar-H), 7.06 (1H, d, J = 2.0Hz, Ar-H), 4.60 (1H, br s, -NHBOC), 4.28 (2H, s, Ar-CH₂N-), 4.14 (1H, br s, -NH-), 3.45 (2H, q, J = 6.9Hz, -CH₂NHBOC), 3.02 (2H, s, -CH₂-), 2.95 (2H, t, J = 6.9Hz, Ar-CH₂-), 1.43 (9H, s, t-Bu), 1.37 (6H, s, -CMe₂).

3. 3-(2-Aminoethyl)-5-[(4,4-dimethyl-1,1-dioxo-1,2,5-thiadiazolidin-2-yl)methyl]-1H-indole

The title compound was prepared from the product from step 2 using the conditions described for Example 1 (step 2); colourless thick oil; δ_H (360MHz, CDCl₃) 8.09 (1H, br s, indole N-H), 7.58 (1H, s, Ar-H), 7.35 (1H, d, J = 8.4Hz, Ar-H), 7.21 (1H, dd, J = 8.4 and 1.5Hz, Ar-H), 7.08 (1H, d, J = 2.1Hz, Ar-H), 4.27 (2H, s, Ar-CH₂N-), 3.03 (2H, t, J = 6.6Hz, -CH₂NH₂), 3.01 (2H, s, -CH₂-), 2.90 (2H, t, J = 6.6Hz, Ar-CH₂-), 1.36 (6H, s, -CMe₂).

EXAMPLE 193-(2-Aminoethyl)-5-[(3,3-dimethyl-1,1-dioxo-1,2,5-thiadiazolidin-2-yl)methyl]-1H-indole1. 2-Tert-butyloxycarbonyl-4,4-dimethyl-1,2,5-thiadiazolidine-1,1-dioxide

To a stirred solution of 3,3-dimethyl-1,2,5-thiadiazolidine-1,1-dioxide (2.5g, 16.6mmol) in anhydrous dimethylformamide (50ml) was added sodium hydride (60% dispersion in oil; 666mg) in two portions. After being stirred at 40°C for 50 minutes under nitrogen, the mixture was allowed to cool to room temperature, diluted with anhydrous dimethylformamide (20ml) and treated with di-tert-butyldicarbonate (3.99g, 18.26mmol). After 1 hour 45 minutes of stirring at room temperature, the mixture was diluted with water (200ml) and extracted with diethyl ether (3 x 100ml). The organic phases were washed with brine (2 x 50ml), dried (MgSO₄) and concentrated. Flash chromatography of the residue (silica gel, dichloromethane to dichloromethane-diethyl ether 50:50) gave a mixture of the required product and 2,5-di-tert-butyloxycarbonyl-3,3-dimethyl-1,2,5-thiadiazolidine-1,1-dioxide. Trituration of this mixture with hot hexane afforded 1.26g (30%) of the required title compound as a white solid; δ_H (250MHz, CDCl₃) 4.39 (1H, br s, -NH-), 3.70 (2H, s, -CH₂-), 1.54 (9H, s, t-Bu), 1.47 (6H, s, -CMe₂); m/z (CI) 249 (M⁺-1).

2. 3-[2-(N-Tert-butyloxycarbonylamino)ethyl]-5-[(2-tert-butyloxycarbonyl-4,4-dimethyl-1,2,5-thiadiazolidin-5-yl)methyl]-1H-indole

The title compound was prepared in 84% yield from Intermediate 3 and 2-tert-butyloxycarbonyl-4,4-dimethyl-1,2,5-thiadiazolidine-1,1-dioxide using a similar method to that described for Example 18 (step 2); white foam; δ_H (250MHz, CDCl₃) 8.04 (1H, br s, indole N-H), 7.58 (1H, s, Ar-H), 7.32 (2H, s, Ar-H), 7.02 (1H, d, J = 2.2Hz, Ar-H), 4.59 (1H, br s, -NH-), 4.36 (2H, s, Ar-CH₂N-), 3.59 (2H, s, -CH₂-), 3.45 (2H, br q, J = 6.3Hz, -CH₂NH-), 2.94 (2H, t, J = 6.3Hz, Ar-CH₂-), 1.55 (9H, s, t-Bu), 1.43 (9H, s, t-Bu), 1.30 (6H, s, -CMe₂); m/z (FAB) 523 (M⁺+1).

3. 3-(2-Aminoethyl)-5-[(3,3-dimethyl-1,1-dioxo-1,2,5-thiadiazolidin-2-yl)methyl]-1H-indole

A solution of the product from step 2 (450mg) in 90% formic acid (18ml) was stirred at room temperature for 1 hour and at 40°C for 1 hour 20 minutes. The solvent was removed under vacuum and the residue was purified by flash chromatography (silica gel, dichloromethane-methanol-ammonia 80:20:2) to give 175mg (63%) of the title compound as a colourless thick oil; δ_H (360MHz, CDCl₃) 8.04 (1H, br s, indole N-H), 7.61 (1H, s, Ar-H), 7.32 (1H, d, J = 8.3Hz, Ar-H), 7.28 (1H, dd, J = 8.3 and 1.4Hz, Ar-H), 7.04 (1H, s, Ar-H), 4.37 (2H, s, Ar-CH₂N-), 3.26 (2H, s, -CH₂-), 3.01 (2H, t, J = 6.6Hz -CH₂NH₂), 2.90 (2H, t, J = 6.6Hz, Ar-CH₂-), 1.22 (6H, s, -CMe₂); m/z (CI) 323 (M⁺+1).

EXAMPLE 203-(2-Aminoethyl)-5-(1,1-dioxo-5-methyl-1,2,5-thiadiazolidin-2-yl)-1H-indole1. 4-(1,1-dioxo-5-methyl-1,2,5-thiadiazolidine-2-yl)nitrobenzene

To a solution of 2-methyl-1,2,5-thiadiazolidine-1,1-dioxide (2.02g, 14.8mmol) in anhydrous dimethylformamide (30ml) was added sodium hydride (60% dispersion in oil; 0.59g) and the mixture was stirred at room temperature under nitrogen for 40 minutes. A solution of 1-fluoro-4-nitrobenzene (2.09g, 14.8mmol) in anhydrous dimethylformamide (15ml) was added to the above solution and the mixture was refluxed for 1 hour. Water (200ml) was added and products were extracted with ethyl acetate (2 x 150ml), dried (MgSO₄) and concentrated to an orange solid. Crystallisation from ethyl acetate (150ml) afforded 2.61g (68.7%) of

the title compound as a pale orange solid; mp 155-163 °C; δ_H (250MHz, DMSO-d₆) 8.29 (2H, d, J = 9.3Hz, Ar-H), 7.34 (2H, d, J = 9.3Hz, Ar-H), 4.00 (2H, t, J = 6.4Hz, -CH₂-), 3.57 (2H, t, J = 6.4Hz, -CH₂-), 2.78 (3H, s, -CH₃); m/z (EI) 257 (M⁺).

5 2. 4-(1,1-dioxo-5-methyl-1,2,5-thiadiazolidin-2-yl)aniline hydrochloride

A suspension of the previous compound (2.56g) in a mixture of ethanol (80ml), ethyl acetate (40ml) and 2N hydrochloric acid (5.22ml) was hydrogenated at 30 psi over 10% palladium on carbon (0.25g) for 45 minutes. The catalyst was filtered off, washed with absolute ethanol and solvents were removed under vacuum to give a crude product (0.64g) which was dissolved in water (100ml) and washed with diethyl ether (2 x 50ml) to eliminate a less polar impurity. Further washings of the catalyst with water (100ml) afforded extra pure title compound which was combined with the previous aqueous phase and concentrated to give a combined yield of 2.43g (92.6%) as a pale purple solid; δ_H (250MHz, D₂O) 7.42 (4H, m, Ar-H), 3.96 (2H, t, J = 6.3Hz, -CH₂-), 3.60 (2H, t, J = 6.3Hz, -CH₂-), 2.86 (3H, s, -CH₃); m/z (EI) 227 (M⁺).

15

3. 4-(1,1-dioxo-5-methyl-1,2,5-thiadiazolidin-2-yl)phenylhydrazine hydrochloride

The title compound was prepared in 96% yield from 4-(1,1-dioxo-5-methyl-1,2,5-thiadiazolidin-2-yl)-aniline hydrochloride using a similar method to that described for Intermediate 1 (step 1); yellow solid; δ_H - (360MHz, DMSO-d₆) 7.15 (2H, d, J = 8.9Hz, Ar-H), 6.92 (2H, d, J = 8.9Hz, Ar-H), 3.74 (2H, t, J = 6.4Hz, -CH₂-), 3.42 (2H, t, J = 6.4Hz, -CH₂-), 2.68 (3H, s, -CH₃); m/z (FAB) 243 (M⁺ + 1).

4. 3-(2-Aminoethyl)-5-(1,1-dioxo-5-methyl-1,2,5-thiadiazolidin-2-yl)-1H-indole

25 A solution of the previous hydrazine hydrochloride (1.45g, 4.95mmol) and 4-chlorobutanal dimethylacetal (0.75g, 4.95mmol) in a mixture of absolute ethanol (50ml) and water (10ml) was refluxed under nitrogen for 3 hours. Solvents were removed under vacuum and the residue was purified by flash chromatography (silica gel, dichloromethane-methanol-ammonia 60:8:1 to 40:8:1) to give 159mg (11%) of the title compound as a thick oil; δ_H (360MHz, DMSO-d₆) 10.9 (1H, br s, indole N-H), 7.41 (1H, d, J = 2.1Hz, Ar-H), 7.35 (1H, d, J = 8.5Hz, Ar-H), 7.19 (1H, s, Ar-H), 7.08 (1H, dd, J = 8.5 and 2.1Hz, Ar-H), 3.84 (2H, t, J = 6.3Hz, -CH₂-), 3.44 (2H, t, J = 6.3Hz, -CH₂-), 2.88-2.74 (4H, m, CH₂CH₂NH₂), 2.72 (3H, s, -NMe).

EXAMPLE 21

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3-(2-Aminoethyl)-5-(5-benzyl-1,1-dioxo-1,2,5-thiadiazolidin-2-yl)-1H-indole

1. 2-Benzyl-1,2,5-thiadiazolidine-1,1-dioxide

40 To a refluxing solution of sulfamide (27.12g, 282mmol) in anhydrous pyridine (250ml) was added dropwise N-benzylenediamine (42.4ml, 282mmol) over 3 hours. The resulting solution was refluxed under nitrogen for a further 16 hours before the solvent was removed under vacuum. The residue was dissolved in dichloromethane (100ml) and washed with 2N hydrochloric acid (1 x 100ml). The aqueous layer was extracted with dichloromethane (2 x 100ml) and the combined organic solutions were washed with brine (50ml), dried (Na₂SO₄) and concentrated. Flash chromatography of the residue (silica gel, dichloromethane-methanol 95:5) gave 47.3g (79%) of the title compound as a white solid; δ_H (360MHz, CDCl₃) 7.32 (5H, m, Ph), 4.34 (1H, br s, -NH-), 4.18 (2H, s, Ar-CH₂N-), 3.47 (2H, q, J = 6.4Hz, -CH₂NH-), 3.27 (2H, t, J = 6.4Hz, -CH₂-); m/z (CI) 213 (M⁺ + 1).

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2. 4-(5-Benzyl-1,1-dioxo-1,2,5-thiadiazolidin-2-yl)nitrobenzene

The title compound was prepared in 79% yield from 2-benzyl-1,2,5-thiadiazolidine-1,1-dioxide and 1-fluoro-4-nitrobenzene using a similar method to that described for Example 20 (step 1). The crude product was crystallised from ethyl acetate to give a yellow solid; mp 164-165 °C; δ_H (360MHz, DMSO-d₆) 8.30 (2H, d, J = 9.2Hz, Ar-H), 7.40 (5H, m, Ph), 7.33 (2H, d, J = 9.2Hz, Ar-H), 4.31 (2H, s, PhCH₂-), 3.98 (2H, t, J = 6.4Hz, -CH₂-), 3.49 (2H, t, J = 6.4Hz, -CH₂-); m/z (EI) 333 (M⁺).

3. 4-(5-Benzyl-1,1-dioxo-1,2,5-thiadiazolidin-2-yl)aniline hydrochloride

A solution of the previous nitro compound (5.08g) in a mixture of ethanol (20ml), ethyl acetate (100ml), water (8ml) and 1N hydrochloric acid (16ml) was hydrogenated at 30 psi over 10% palladium on carbon for 25 minutes. The catalyst was filtered off, washed with ethanol and water and solvents were removed under vacuum. The residue was crystallised from a mixture of ethanol (150ml) and water (5ml) to give 3.19g
 5 (61%) of the title compound; δ_H (250MHz, DMSO-d₆) 7.44-7.27 (9H, m, Ph and Ar-H), 4.25 (2H, s, PhCH₂-), 3.83 (2H, t, J = 6.4Hz, -CH₂-), 3.42 (2H, t, J = 6.4Hz, -CH₂-).

4. 4-(5-Benzyl-1,1-dioxo-1,2,5-thiadiazolidin-2-yl)phenylhydrazine hydrochloride

10 The title compound was prepared from 4-(5-benzyl-1,1-dioxo-1,2,5-thiadiazolidin-2-yl)aniline hydrochloride by a similar method to that described for Intermediate 1 (step 1); pale brown solid; δ_H (250MHz, DMSO-d₆) 7.42-7.32 (5H, m, Ph), 7.24 (2H, d, J = 8.5Hz, Ar-H), 7.02 (2H, d, J = 8.5Hz, Ar-H), 4.24 (2H, s, PhCH₂-), 3.68 (2H, t, J = 6.4Hz, -CH₂-), 3.39 (2H, t, J = 6.4Hz, -CH₂-).

15 5. 3-(2-Aminoethyl)-5-(5-benzyl-1,1-dioxo-1,2,5-thiadiazolidin-2-yl)-1H-indole

The title compound was prepared in 8% yield from the previous hydrazine hydrochloride and 4-chlorobutanal dimethylacetal using the conditions described for Example 20 (step 4); brown solid; δ_H - (250MHz, DMSO-d₆) 10.91 (1H, br s, indole N-H), 7.45-7.33 (7H, m, Ph and Ar-H), 7.20 (1H, s, Ar-H), 7.12 (1H, dd, J = 8.7 and 2.1Hz, Ar-H), 4.24 (2H, s PhCH₂-), 3.84 (2H, t, J = 6.3Hz, -CH₂-), 3.37 (2H, t, J = 6.3Hz, -CH₂-), 2.80 (4H m, -CH₂CH₂NH₂).

20 Examples 22 to 25 were prepared from the products of Examples 18 to 21 respectively using a similar method to that described for Example 2.

25 EXAMPLE 22

3-[2-(Dimethylamino)ethyl]-5-[(4,4-dimethyl-1,1-dioxo-1,2,5-thiadiazolidin-2-yl)methyl]-1H-indole. Succinate

The succinate salt was prepared and recrystallised from ethanol-diethyl ether; mp 149-151°C; δ_H - (360MHz, DMSO-d₆) 10.85 (1H, s, indole N-H), 7.50 (1H, s, Ar-H), 7.32 (1H, d, J = 8.3Hz, Ar-H), 7.18 (1H, s, Ar-H), 7.06 (1H, dd, J = 8.3 and 1.4Hz, Ar-H), 4.10 (2H, s, Ar-CH₂N-), 2.93 (2H, s, -CH₂-), 2.87 (2H, t, J = 8.5Hz, -CH₂-), 2.71 (2H, t, J = 8.5Hz, -CH₂-), 2.37 (6H, s, -NMe₂), 2.36 (4H, s, succinic acid), 1.23 (6H, s, -CMe₂); m/z (EI) 350 (M⁺). (Found: C, 53.49; H, 6.55; N, 11.74. C₁₇H₂₆N₄O₂S x 1.0 C₄H₆O₄ requires: C, 53.83; H, 6.88; N, 11.96%).

35

EXAMPLE 23

3-[2-(Dimethylamino)ethyl]-5-[(3,3-dimethyl-1,1-dioxo-1,2,5-thiadiazolidin-2-yl)methyl]-1H-indole. Succinate

40 The succinate salt was prepared and recrystallised from ethanol-diethyl ether; mp 164-166°C; δ_H - (360MHz, DMSO-d₆) 10.76 (1H, br s, indole N-H), 7.52 (1H, s, Ar-H), 7.30-7.25 (2H, m, Ar-H and -NH-), 7.13 (1H, s, Ar-H), 7.12 (1H, d, J = 8.5Hz, Ar-H), 4.21 (2H, s, Ar-CH₂N-), 3.09 (2H, d, J = 7.1Hz, -CH₂-), 2.83 (2H, t, J = 8.4Hz, -CH₂-), 2.65 (2H, t, J = 8.4Hz, -CH₂-), 2.34 (2H, s, succinic acid), 2.32 (6H, s, -NMe₂), 1.14 (6H, s, -CMe₂); m/z (CI) 351 (M⁺ + 1). (Found: C, 55.89; H, 6.92; N, 13.59. C₁₇H₂₆N₄O₂S x 0.5 C₄N₆O₄ requires: C, 55.72; H, 7.14; N, 13.68%).

EXAMPLE 24

3-[2-(Dimethylamino)ethyl]-5-(1,1-dioxo-5-methyl-1,2,5-thiadiazolidin-2-yl)-1H-indole. Oxalate

50

The oxalate salt was prepared and recrystallised from methanol-diethyl ether; mp 169-176°C; δ_H - (360MHz, D₂O) 7.62 (1H, d, J = 2.0Hz, Ar-H), 7.58 (1H, d, J = 8.7Hz, Ar-H), 7.38 (1H, s, Ar-H), 7.26 (1H, dd, J = 8.7 and 2.1Hz, Ar-H), 3.95 (2H, t, J = 6.3Hz, -CH₂-), 3.59 (2H, t, J = 6.3Hz, -CH₂-), 3.46 (2H, t, J = 7.4Hz, -CH₂-), 3.20 (2H, t, J = 7.4Hz, -CH₂-), 2.90 (6H, s, -NMe₂), 2.86 (3H, s, -CH₃); m/z (CI) 323 (M⁺ + 1). (Found: C, 48.60; H, 5.73; N, 13.37. C₁₅H₂₂N₄O₂S x 1.0 C₂H₂O₄ x 0.3 H₂O requires: C, 48.86; H, 5.93; N, 13.41%).

EXAMPLE 25

3-[2-(Dimethylamino)ethyl]-5-(5-benzyl-1,1-dioxo-1,2,5-thiadiazolidin-2-yl)-1H-indole. Oxalate

The oxalate salt was prepared and recrystallised from methanol; mp 157-165 °C; δ_H (360MHz, DMSO-d₆) 11.09 (1H, br s, indole N-H), 7.51 (1H, s, Ar-H), 7.45-7.32 (6H, m, Ph and Ar-H), 7.30 (1H, s, Ar-H), 7.18 (1H, dd, J = 8.0 and 1.4Hz, Ar-H), 4.24 (2H, s, PhCH₂-), 3.86 (2H, t, J = 6.3Hz, -CH₂-), 3.38 (2H, t, J = 6.3Hz, -CH₂-), 3.26 (2H, m, -CH₂-), 3.05 (2H, m, -CH₂-), 2.80 (6H, s, -NMe₂); m/z (EI) 398 (M⁺). (Found: C, 55.32; H, 5.87; N, 11.05. C₂₁H₂₆N₄O₂S x 1.0 C₂H₂O₄ x 0.6 H₂O requires: C, 55.32; H, 5.89; N, 11.22%).

EXAMPLE 26

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Tablet Preparation

Tablets containing 1.0, 2.0, 25.0, 26.0, 50.0 and 100.0mg, respectively of the following compounds are prepared as illustrated below:

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- 3-[2-(Dimethylamino)ethyl]-5-[(1,1-dioxo-5-methyl-1,2,5-thiadiazolidin-2-yl)methyl]-1H-indole. Succinate
 3-[2-(Dimethylamino)ethyl]-5-[(1,1-dioxo-6-methyl-3,4,5,6-tetrahydro-1,2,6-thiadiazin-2-yl)methyl]-1H-indole.
 Oxalate

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TABLE FOR DOSES CONTAINING FROM 1-25MG OF THE ACTIVE COMPOUND

| | Amount-mg | | |
|----------------------------|-----------|-------|-------|
| Active Compound | 1.0 | 2.0 | 25.0 |
| Microcrystalline cellulose | 49.25 | 48.75 | 37.25 |
| Modified food corn starch | 49.25 | 48.75 | 37.25 |
| Magnesium stearate | 0.50 | 0.50 | 0.50 |

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TABLE FOR DOSES CONTAINING FROM 26-100MG OF THE ACTIVE COMPOUND

| | Amount-mg | | |
|----------------------------|-----------|-------|-------|
| Active Compound | 26.0 | 50.0 | 100.0 |
| Microcrystalline cellulose | 52.0 | 100.0 | 200.0 |
| Modified food corn starch | 2.21 | 4.25 | 8.5 |
| Magnesium stearate | 0.39 | 0.75 | 1.5 |

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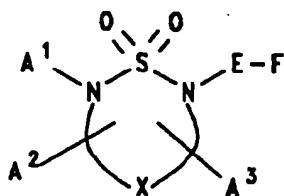
All of the active compound, cellulose, and a portion of the corn starch are mixed and granulated to 10% corn starch paste. The resulting granulation is sieved, dried and blended with the remainder of the corn starch and the magnesium stearate. The resulting granulation is then compressed into tablets containing 1.0mg, 2.0mg, 25.0mg, 26.0mg, 50.0mg and 100mg of the active ingredient per tablet.

Claims

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1. A compound of formula I, or a salt or prodrug thereof:

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(1)

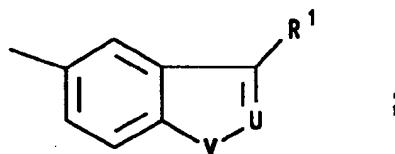
wherein

-X- represents $-(CH_2)_m-$ in which m is 2 or 3;
 A¹ represents hydrogen, hydrocarbon or a heterocyclic group;
 A² and A³ independently represent hydrogen or C₁₋₆ alkyl;

5 E represents a bond or a straight or branched alkylene chain containing from 1 to 4 carbon atoms;
 and

F represents a group of formula

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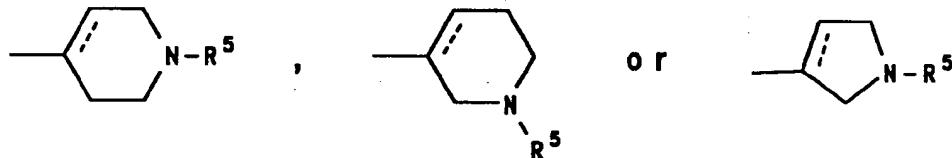


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in which

U represents nitrogen or C-R²;
 20 V represents oxygen, sulphur or N-R³;
 R¹ represents $-(CH_2)_pCHR^4.NR^6R^7$ or a group of formula

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in which the broken line represents an optional chemical bond;

p is 1 or 2; and

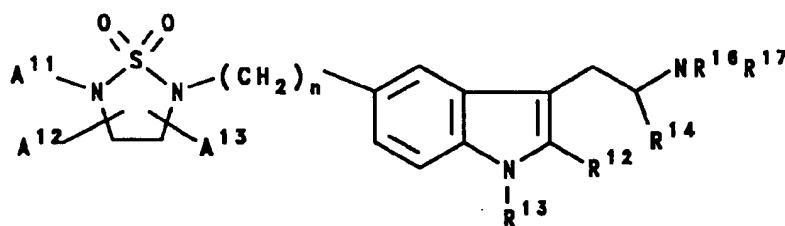
R², R³, R⁴, R⁵, R⁶ and R⁷ independently represent hydrogen or C₁₋₆ alkyl.

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2. A compound as claimed in claim 1 wherein one of A² and A³ represents hydrogen and the other represents hydrogen or C₁₋₆ alkyl.
3. A compound as claimed in claim 1 or claim 2 wherein R¹ represents aminoethyl, N-methylaminoethyl, N,N-dimethylaminoethyl, 4-piperidyl, 1-methyl-4-piperidyl, 3-pyrrolidinyl or 1-methyl-3-pyrrolidinyl.
- 40 4. A compound as claimed in claim 1 represented by formula IIA, and salts and prodrugs thereof:

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(IIA)

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wherein

n is zero, 1, 2 or 3;

A^{11} represents hydrogen; or C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, aryl, aryl-(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, heteroaryl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted; and

A^{12} , A^{13} , R^{12} , R^{13} , R^{14} , R^{16} and R^{17} independently represent hydrogen or C_{1-6} alkyl.

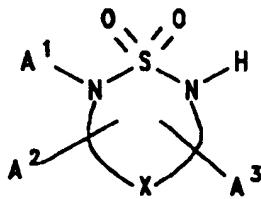
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5. A compound as claimed in claim 4 wherein n is zero, 1 or 2.
6. A compound as claimed in claim 1 selected from:
 3-[2-(dimethylamino)ethyl]-5-[(1,1-dioxo-5-methyl-1,2,5-thiadiazolidin-2-yl)methyl]-1H-indole;
 3-(2-aminoethyl)-5-[(1,1-dioxo-5-methyl-1,2,5-thiadiazolidin-2-yl)methyl]-1H-indole;
 3-[2-(dimethylamino)ethyl]-5-[2-(1,1-dioxo-5-methyl-1,2,5-thiadiazolidin-2-yl)ethyl]-1H-indole;
 3-(2-aminoethyl)-5-[2-(1,1-dioxo-5-methyl-1,2,5-thiadiazolidin-2-yl)ethyl]-1H-indole;
 3-[2-(dimethylamino)ethyl]-5-[(5-(4-acetylaminobenzyl)-1,1-dioxo-1,2,5-thiadiazolidin-2-yl)methyl]-1H-indole;
 3-(2-aminoethyl)-5-[(5-(4-acetylaminobenzyl)-1,1-dioxo-1,2,5-thiadiazolidin-2-yl)methyl]-1H-indole;
 3-(2-aminoethyl)-5-[(1,1-dioxo-1,2,5-thiadiazolidin-2-yl)methyl]-1H-indole;
 3-(2-aminoethyl)-5-[(1,1-dioxo-5-isopropyl-1,2,5-thiadiazolidin-2-yl)methyl]-1H-indole;
 3-(2-aminoethyl)-5-[2-(1,1-dioxo-1,2,5-thiadiazolidin-2-yl)ethyl]-1H-indole;
 3-(2-aminoethyl)-5-[2-(1,1-dioxo-5-ethyl-1,2,5-thiadiazolidin-2-yl)ethyl]-1H-indole;
 3-[2-(dimethylamino)ethyl]-5-[(1,1-dioxo-1,2,5-thiadiazolidin-2-yl)methyl]-1H-indole;
 3-[2-(dimethylamino)ethyl]-5-[(1,1-dioxo-5-isopropyl-1,2,5-thiadiazolidin-2-yl)methyl]-1H-indole;
 3-[2-(dimethylamino)ethyl]-5-[2-(1,1-dioxo-1,2,5-thiadiazolidin-2-yl)ethyl]-1H-indole;
 3-[2-(dimethylamino)ethyl]-5-[2-(1,1-dioxo-5-ethyl-1,2,5-thiadiazolidin-2-yl)ethyl]-1H-indole;
 3-[2-(methylamino)ethyl]-5-[(1,1-dioxo-5-methyl-1,2,5-thiadiazolidin-2-yl)methyl]-1H-indole;
 3-(2-aminoethyl)-5-[(1,1-dioxo-6-methyl-3,4,5,6-tetrahydro-1,2,6-thiadiazin-2-yl)methyl]-1H-indole;
 3-[2-(dimethylamino)ethyl]-5-[(1,1-dioxo-6-methyl-3,4,5,6-tetrahydro-1,2,6-thiadiazin-2-yl)methyl]-1H-indole;
 3-(2-aminoethyl)-5-[(4,4-dimethyl-1,1-dioxo-1,2,5-thiadiazolidin-2-yl)methyl]-1H-indole;
 3-(2-aminoethyl)-5-[(3,3-dimethyl-1,1-dioxo-1,2,5-thiadiazolidin-2-yl)methyl]-1H-indole;
 3-(2-aminoethyl)-5-(1,1-dioxo-5-methyl-1,2,5-thiadiazolidin-2-yl)-1H-indole;
 3-(2-aminoethyl)-5-(5-benzyl-1,1-dioxo-1,2,5-thiadiazolidin-2-yl)-1H-indole;
 3-[2-(dimethylamino)ethyl]-5-[(4,4-dimethyl-1,1-dioxo-1,2,5-thiadiazolidin-2-yl)methyl]-1H-indole;
 3-[2-(dimethylamino)ethyl]-5-[(3,3-dimethyl-1,1-dioxo-1,2,5-thiadiazolidin-2-yl)methyl]-1H-indole;
 3-[2-(dimethylamino)ethyl]-5-(1,1-dioxo-5-methyl-1,2,5-thiadiazolidin-2-yl)-1H-indole;
 3-[2-(dimethylamino)ethyl]-5-(5-benzyl-1,1-dioxo-1,2,5-thiadiazolidin-2-yl)-1H-indole;
 and salts and prodrugs thereof.
7. A pharmaceutical composition comprising a compound as claimed in any one of the preceding claims in association with a pharmaceutically acceptable carrier or excipient.
8. A compound as claimed in any one of claims 1 to 6 for use in therapy.
9. The use of a compound as claimed in any one of claims 1 to 6 for the manufacture of a medicament for the treatment and/or prevention of clinical conditions for which a selective agonist of 5-HT₁-like receptors is indicated.
10. A process for the preparation of a compound as claimed in any one of claims 1 to 6 which comprises:
 (A) reacting a compound of formula W-E-F with a compound of formula III:

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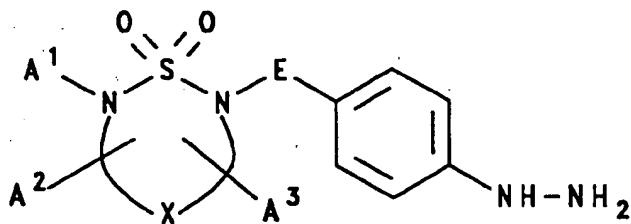
(III)

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wherein X, A¹, A², A³, E and F are as defined in claim 1, and W represents a group which is capable of being displaced during the course of the reaction; or
 (B) reacting a compound of formula XII:

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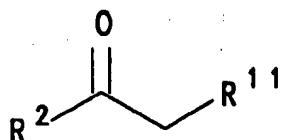


(XII)

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wherein X, A¹, A², A³ and E are as defined in claim 1; with a compound of formula V or a carbonyl-protected form thereof:

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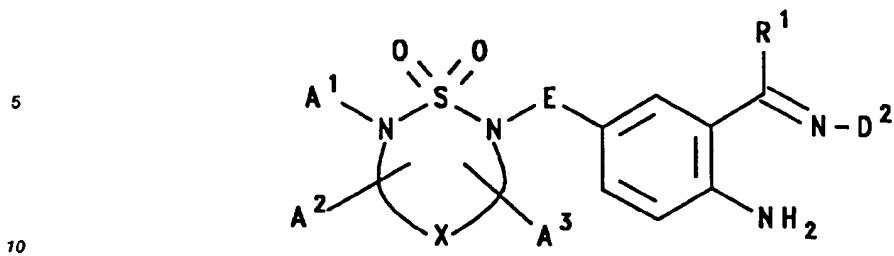
(V)

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wherein R² is as defined in claim 1 and R¹¹ corresponds to the group R¹ as defined in claim 1 or represents a group of formula -CH₂.CHR⁴D¹, in which R⁴ is as defined in claim 1 and D¹ represents a readily displaceable group; followed, where required, by N-alkylation by standard methods to introduce the moiety R³; or
 (C) cyclising a compound of formula XVII:

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(XVII)

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wherein X, A¹, A², A³, E and R¹ are as defined in claim 1, and D² represents a readily displaceable group; followed, where required, by N-alkylation by standard methods to introduce the moiety R³; and

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(D) subsequently, where appropriate, converting a compound of formula I initially obtained into a further compound of formula I by conventional methods.

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European Patent
Office

EUROPEAN SEARCH REPORT

Application Number

EP 92 20 0475

| DOCUMENTS CONSIDERED TO BE RELEVANT | | | |
|--|---|---|--|
| Category | Citation of document with indication, where appropriate, of relevant passages | Relevant to claim | CLASSIFICATION OF THE APPLICATION (Int. Cl.5) |
| D,A | EP-A-0 313 397 (THE WELLCOME FOUNDATION LIMITED) * the whole document * --- | 1,7-9 | C07D417/04 C07D417/06 C07D417/14 A61K31/41 A61K31/53 |
| D,A | GB-A-2 083 463 (GLAXO GROUP LIMITED) * the whole document * --- | 1,7-9 | |
| | | | TECHNICAL FIELDS SEARCHED (Int. Cl.5) |
| | | | C07D |
| The present search report has been drawn up for all claims | | | |
| Place of search | Date of completion of the search | Examiner | |
| THE HAGUE | 02 JUNE 1992 | ALLARD M.S. | |
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| EPO FORM 150 (02/82) (Rev. 1) | | | |